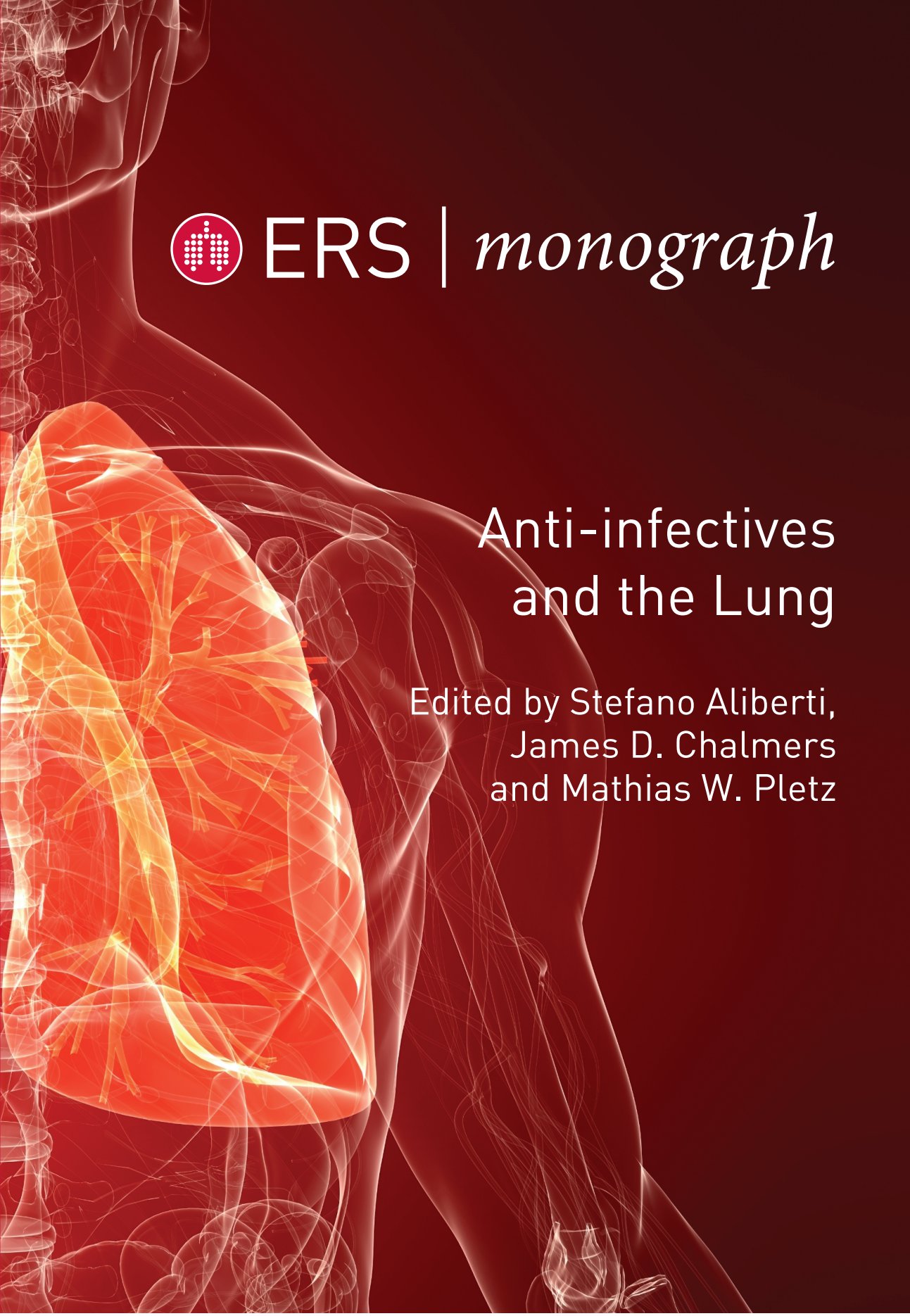

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Anti-infectives and the Lung

Edited by Stefano Aliberti, James D. Chalmers and Mathias W. Pletz

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Edited by
Stefano Aliberti, James D. Chalmers
and Mathias W. Pletz

Editor in Chief
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Tel: 44 114 2672860 | E-mail: Monograph@ersj.org.uk

Published by European Respiratory Society ©2017
March 2017
Print ISBN: 978-1-84984-083-5
Online ISBN: 978-1-84984-084-2
Print ISSN: 2312-508X
Online ISSN: 2312-5098
Typesetting by Nova Techset Private Limited
Printed by Ashford Colour Press Limited

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March 2017

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Preface

Robert Bals

The use and prescription of antibiotics is an area of discussion, insecurities, a multitude of guidelines, a number of novel drugs and one of the most frequent medical interventions. The clinical spectrum of patients with infections of the respiratory tract is wide, and covers disease entities such as viral infections presenting as a common cold, "standard" CAP and pneumogenic sepsis with multiresistant microorganisms. While respiratory infections are among the most frequent diseases in pulmonary medicine, a number of problem areas are obvious: 1) there is often a lack of evidence-based approaches to therapy; 2) the role of novel antibiotics is not well defined; 3) the number of resistant microorganisms is increasing for a variety of reasons, from false application in patients to misuse in animal husbandry; and 4) the inadequate use of anti-infectives can cause significant harm.

With this *ERS Monograph*, we provide the reader with a broad and detailed overview on anti-infective drugs in pulmonary care. Several chapters focus on the pharmacology and clinical use of specific antibiotics or antifungals. Other chapters go into more detail on specific disease entities, such as asthma, COPD, pleural infections, TB and CAP. In addition, the book discusses current topics that cover subjects of broad importance, including resistance mechanisms, inhaled application of antibiotics, antibiotic stewardship, long-term treatment and novel drug developments.

The Guest Editors, Stefano Aliberti, James D. Chalmers and Mathias W. Pletz, have worked very successfully to select these topics and to integrate these aspects into this *ERS Monograph* that summarises our current knowledge. I thank the Guest Editors and all of the authors for their excellent work. Together, they have produced a practice-guideline publication that comprises information on the scientific background and the application at the patient's bedside. I am sure that this comprehensive overview will be useful for the clinical practice of

Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

a broad range of respiratory physicians and improve the care for patients with pulmonary infections.

Disclosures: R. Bals has received grants from the German Research Ministerium and the Deutsche Forschungsgemeinschaft. He has also received personal fees from GSK, AstraZeneca, Boehringer Ingelheim and CSL Behring.

Guest Editors

Stefano Aliberti

Stefano Aliberti is Associate Professor in Respiratory Medicine at the University of Milan and consultant at the Policlinico Hospital in Milan (Italy). His major clinical and research interests are in chronic and acute respiratory infections. He started working on CAP in the mid-2000s at the University of Louisville (KY, USA) as an investigator of the Community-Acquired Pneumonia Organization (CAPO) and member of the Community-Acquired Pneumonia Inflammatory Study Group (CAPISG). He has extensively published clinical and translational research papers on CAP, especially in the field of antimicrobial resistance, and was awarded the Young Researcher Award in Respiratory Infections from the European Respiratory Society (ERS) in 2007.

In recent years he has been heavily involved in bronchiectasis research, leading the largest non-cystic fibrosis bronchiectasis clinic in Italy. He co-founded the European Bronchiectasis Registry (EMBARC), and is the Director of the Italian Bronchiectasis Registry and the Italian Registry of Pulmonary Non-tuberculous Mycobacteria.

Stefano Aliberti has published over 130 articles on respiratory infections over the past 10 years. He is an Associate Editor of *ERJ Open Research* and *BMC Pulmonary Medicine*. He has been involved in the ERS, as Secretary of the Respiratory Infections Group, and Secretary and now Head of the Respiratory Infections Assembly.

James D. Chalmers

James D. Chalmers is Clinical Senior Lecturer and Honorary Consultant at the University of Dundee (UK). He trained in Glasgow and Edinburgh (UK), performing his PhD studies at the Medical Research Council (MRC) Centre for Inflammation Research studying the immunology of bronchiectasis. His research and clinical interests are in respiratory infections, including bronchiectasis, COPD and CAP.

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He runs a translational research group primarily focused on developing novel diagnostics and treatments for respiratory infections, with current major programmes looking at neutrophilic inflammation and the microbiome in bronchiectasis, COPD and severe asthma. He is a co-founder and Chair of EMBARC.

James D. Chalmers has published over 120 papers in peer-reviewed journals since 2008, and has received prestigious research and teaching awards from the British Thoracic Society, ERS and Royal College of Physicians. He is an Associate Editor of the *European Respiratory Journal*, a member of the International Advisory Board of *Lancet Respiratory Medicine*, Secretary of the European Board for Accreditation in Pneumology, Chair of the British Thoracic Society Respiratory Infections Speciality Advisory Group and holds a number of other major society/committee appointments.

Mathias W. Pletz

Mathias W. Pletz, Professor for Infectious Diseases, is a board-certified physician for internal medicine, pulmonology and infectious diseases, and the Head of the Center for Infectious Diseases and Infection Control of the University Hospital in Jena (Germany). He also leads a clinical research group focusing on novel diagnostic and therapeutic strategies against MDR bacterial pathogens, funded by the German Ministry for Science and Education.

Mathias W. Pletz received his PhD in Virology at the University of Leipzig (Germany). During his thesis he worked as a guest researcher at the Food and Drug Administration Laboratory of Parasitic Pathology and Biochemistry (Bethesda, MD, USA). After his medical training at the University of Leipzig, Baylor College of Medicine (Houston, TX, USA) and the University of Basel (Switzerland), he started his residency at the Chest Hospital in Berlin (Germany). Subsequently, he spent 2 years as a postdoctoral researcher at Emory University (Atlanta, GA, USA) working with Keith Klugman's group on the spread of multiresistant pneumococci. In addition, he served as a guest researcher at the Centers for Disease Control and Prevention (CDC) in Atlanta, exploring the severe acute respiratory syndrome (SARS) epidemics. After his return to Germany, he finished his medical training at the Dept of Respiratory Medicine at the Hannover Medical School.

Mathias W. Pletz is the Deputy Director of the German Competence Network for Community-Acquired Pneumonia (CAPNETZ), a member of the Board of Directors of the German Society for Infectious Diseases (DGI) and scientific

https://doi.org/10.1183/2312508X.10000917

advisor for the German Robert Koch Institute. He has published more than 180 papers on pneumonia, pneumococcal vaccines, respiratory infections, antimicrobial resistance and pharmacokinetics of antibiotics in the critically ill. He has also received numerous scientific awards, *e.g.* the Honor Award Certificate from the CDC, the Kass Award of the Infectious Diseases Society of America and the Respiratory Infections Award from the ERS.

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Introduction

Stefano Aliberti[1], James D. Chalmers[2] and Mathias W. Pletz[3,4,5]

On returning from holiday to St Mary's Hospital in London in 1928, Alexander Fleming discovered something unexpected on a Petri dish containing *Staphylococcus*. Contamination of the plate with a rare *Penicillium* fungus led to a zone of bacterial killing, demonstrating that the fungus was secreting a factor that killed staphylococci.

Fleming observed that an extract from this fungus could kill a wide range of bacteria, particularly Gram-positive bacteria. Subsequent work confirmed that some organisms were susceptible to the *Penicillium* extract, while many, particularly Gram-negative organisms, were not. Indeed the initial application of penicillin published in the *British Journal of Experimental Pathology* in June 1929 appeared to be as a method to differentiate between different bacteria in the laboratory [1]. However, in his Nobel Lecture on December 11, 1945, Fleming had already foreseen the "antibiotic resistance crisis" caused by overuse and underdosing [2]:

> *But I would like to sound one note of warning. … It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.*

Thus, through a remarkable accident, one of the greatest medical advances in history was made, *i.e.* the ability to cure disease through antibiotic treatment, and simultaneously the threat of antibiotic resistance was also discovered.

These competing opportunities and threats continue in parallel to this day.

The lung is the key interface between the human body and the microbial world, with an average person with a normal breathing rate inhaling nearly 1 000 000 bacteria per day. It is therefore not surprising that respiratory tract infections are the most common reason for antibiotic prescribing in both primary and secondary care, and a leading cause of mortality worldwide. Despite advances in hygiene and the availability of antimicrobials, TB and pneumonia remain devastating on a global level, while bronchiectasis, cystic fibrosis, pleural

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 https://doi.org/10.1183/2312508X.10001017

infection and NTM disease represent some of the most complex and challenging infectious diseases in medicine.

The correct principles of antibiotic therapy are therefore a critical skill for all practising pulmonologists, primary care physicians, infectious disease specialists and allied health professionals with responsibility for respiratory patients.

It is for this reason we are delighted to introduce this *ERS Monograph* dedicated to understanding the pharmacology, administration, clinical role and stewardship of antibiotics in respiratory disease.

This was a challenging *Monograph* to write and edit. Unlike many aspects of respiratory disease, there are rarely large RCTs to guide our therapy, and respiratory infectious diseases are often neglected in terms of research funding and underestimated in terms of public importance.

In the absence of robust evidence, many antibiotic practices have evolved differently in different countries in Europe and worldwide. A patient presenting with severe CAP in Scandinavia may receive intravenous penicillin, while a patient with the same characteristics might receive piperacillin–tazobactam plus macrolide or vancomycin in the USA. Global antibiotic practices are determined by differences in common organisms and antibiotic resistance patterns, but also more obviously, by cultural attitudes toward the risk of missing a serious infection, perceptions of the importance of antibiotic resistance, concerns over litigation and organisation of healthcare.

We are especially pleased, therefore, that this *ERS Monograph* captures important perspectives from Northern, Southern and Eastern Europe as well as the USA and Japan, among others. The topics cover the major indications for antibiotic use, from LRTIs in the community through to severe infections in critical care. Inhaled delivery is extensively discussed, as is the role of antibiotic therapy in airways diseases such as asthma, COPD and bronchiectasis. Pleural infection, TB, NTM disease and respiratory infections in children are also some of the key highlights.

The first *ERS Monograph* on Antibiotics and the Lung was published in 2004 [3]. A key addition to the current book is that we address the emerging risk of antibiotic resistance with chapters on antimicrobial stewardship and the importance of looking to the future of new drug development to tackle this threat.

After a tumultuous 2016, the authors are writing this Introduction a few days before the inauguration of a new US President in January 2017. You will forgive us then, for paraphrasing from a former US President, from a simpler time, to introduce this new *ERS Monograph*:

> *Ask not what your antibiotics can do for you, ask what you can do for (the responsible use of) antibiotics.*

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Disclosures: J.D. Chalmers has received grants from Aradigm, AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, GSK, Novartis and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, Chiesi, Napp and Pfizer. M.W. Pletz has received grants from the German Research Foundation, the German Ministry for Science and Education, Biotest, InfectoPharm and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Biotest, Clinigen, InfectoPharm, MSD, Pfizer and Thermo Fisher, and has a patent "Measuring antibiotic blood levels with Raman spectroscopy" pending. S. Aliberti has received grants from Bayer Healthcare, Aradigm Corporation, Griffols, European Respiratory Society and Chiesi. He has also received personal fees from Bayer Healthcare, Aradigm Corporation, European Respiratory Society, Griffols, AstraZeneca, Basilea, Zambon, Novartis, Raptor, Chiesi and Actavis UK Ltd.

 https://doi.org/10.1183/2312508X.10001017

List of abbreviations

AUC	area under the curve
BAL	bronchoalveolar lavage
CAP	community-acquired pneumonia
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
ESBL	extended-spectrum β-lactamase
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
ICU	intensive care unit
IFN	interferon
IL	interleukin
LRTI	lower respiratory tract infection
MAC	*Mycobacterium avium* complex
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NTM	nontuberculous mycobacteria
PCR	polymerase chain reaction
PCT	procalcitonin
RCT	randomised controlled trial
TB	tuberculosis
TNF	tumour necrosis factor
VAP	ventilator-associated pneumonia
XDR	extensively drug-resistant

Chapter 1

Antibiotics for pulmonary infections: an overview

Matteo Bassetti and Elda Righi

Pulmonary infections represent an important cause of morbidity and mortality, and require prompt antimicrobial treatment. The correct choice of an empirical regimen is paramount in managing LRTIs due to the difficulty in obtaining a microbial diagnosis. Classic antimicrobials used in the treatment of pulmonary infections include β-lactams (with or without β-lactamase inhibitors), macrolides, tetracyclines and fluoroquinolones. Vancomycin and linezolid are the antimicrobials of choice for the treatment of nosocomial pneumonia caused by MRSA. New compounds have been studied to target pulmonary infections, including those caused by pathogens that are resistant to commonly used antimicrobials. A broad spectrum of activity, penetration into lung tissue, good tolerability, and availability of both oral and intravenous formulations represent key features of the compounds used in the treatment of LRTIs. In this chapter, we summarise the characteristics of commonly used molecules for the treatment of pulmonary infections in adult patients and discuss new options for their treatment.

Cite as: Bassetti M, Righi E. Antibiotics for pulmonary infections: an overview. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 1–20 [https://doi.org/10.1183/2312508X.10004316].

Pulmonary infections are common and represent an important cause of morbidity and mortality [1–3]. LRTIs include acute bronchitis, exacerbation of COPD and pneumonia. Although viruses, and less commonly fungi, can cause LRTIs, bacteria represent the leading pathogens in most infections [4]. Bronchitis can be preceded by a viral upper respiratory tract infection or associated with viral diseases such as influenza. Chronic bronchitis usually presents with persistent cough and sputum production, and is triggered by a combination of environmental factors, such as smoking, and bacterial infections due to *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* [4]. In patients with altered lung structure, such as bronchiectasis, acute exacerbations may be characterised by increased cough, sputum purulence and streaky haemoptysis, and difficult-to-treat pathogens, such as *Pseudomonas* spp., may be involved [4]. The causative agents of pneumonia differ in the community compared with the hospital setting, delineating two clinical entities that require different treatment strategies,

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i.e. CAP and HAP. CAP accounts for up to 600 000 hospital admissions each year in the USA and represents the eighth most common cause of death in the population [5, 6].

Despite recent advances in diagnostic techniques to detect respiratory pathogens, the microbial diagnosis of pulmonary infections remains a challenge. For this reason, the selection of an antimicrobial regimen usually occurs empirically, aiming to include pathogens that are the most likely to be involved. Up to 30% of CAP is caused by *S. pneumoniae*, which represents the most frequent cause across all age groups, followed by *H. influenzae* and atypical bacteria (*e.g. Mycoplasma*, *Chlamydia* and *Legionella* spp.) [7, 8]. Gram-negative bacteria should also be considered as potential causes of severe pneumonia, especially in patients admitted to the ICU [9]. In the ICU, pneumonia is the most prevalent infection and often occurs as VAP [10]. Although the timely choice of an appropriate treatment is of paramount importance in HAP and VAP, antimicrobial therapy is usually empirical, as the identity and susceptibility of the pathogens is often unknown at the time of treatment initiation [11]. Furthermore, an increase in the emergence of MDR pathogens in some areas has been registered in recent decades, hampering the appropriate choice of antimicrobial regimen [12].

Antimicrobials for the treatment of pulmonary infections in adults

Key points for the treatment of LRTIs include the timely initiation and correct selection of empirical antimicrobial therapy and a prompt de-escalation from intravenous (*i.v.*) to oral therapy [13–15]. β-Lactams, in particular penicillins and cephalosporins, as well as macrolides, tetracyclines and fluoroquinolones, are the most commonly used antimicrobials for pulmonary infections in adults.

β-Lactams

Combinations of aminopenicillins and β-lactamase inhibitors (*e.g.* amoxicillin–clavulanate and ampicillin–sulbactam), as well as third- and fourth-generation cephalosporins (*e.g.* ceftriaxone, cefotaxime, ceftazidime and cefepime), are used extensively in the treatment of pulmonary infections. Benzylpenicillin *i.v.* or oral amoxicillin may represent a valid option if penicillin-resistant pneumococci are not documented or suspected [16].

Limitations in the spectrum of these compounds are represented by a low activity against β-lactamase-producing Gram-negative bacteria and MRSA. Piperacillin–tazobactam is often active against ESBL-producing bacteria [17]. Carbapenems, characterised by a wide spectrum, high bactericidal activity and persistent antibiotic effects, are often employed as the last resort in the treatment of MDR pneumonia [18].

The pharmacokinetics of β-lactams is well known. The main parameter defining their antibacterial efficacy is the duration that the free β-lactam concentration is maintained above the MIC ($T_{>MIC}$) [19]. As maximisation of the duration of exposure optimises β-lactam antibacterial effects, extended infusion is usually suggested for these compounds [20]. With the exception of ceftriaxone, which has a long terminal half-life (8–10 h), β-lactams have half-lives of 2–4 h and are eliminated mainly by the kidney, requiring renal adjustments in patients with reduced creatinine clearance [21]. β-Lactams are usually well tolerated, with the main side-effects being gastrointestinal disturbances [22].

 https://doi.org/10.1183/2312508X.10004316

Macrolides

Macrolides bind to the 50S subunit of the 70S ribosome, interfering with protein biosynthesis of bacteria [23]. Compared with erythromycin, clarithromycin and azithromycin are newer macrolides, characterised by rapid absorption [24]. Macrolides are generally well tolerated, although a higher risk for cardiovascular events has been reported compared with β-lactams, especially among elderly patients [25]. Macrolides have also shown immunomodulatory effects that can be beneficial, especially in critically ill patients [26, 27].

Azithromycin is the sole member of the azalide subclass. Compared with erythromycin, azithromycin is acid stable, and is active against *H. influenzae* and *M. catarrhalis* [28]. Azithromycin is inactive against *Pseudomonas* spp. and most aerobic Gram-negative bacilli, while high activity has been demonstrated against atypical pathogens and mycobacteria because of its high intracellular concentrations [29, 30]. Azithromycin has a terminal-phase elimination half-life of ∼60 h, allowing a single-daily-dose regimen. Azithromycin is eliminated predominately through biliary excretion and no dosage adjustments in patients with renal or hepatic dysfunction are required. The clinical efficacy of azithromycin 500 mg once daily has been confirmed in the treatment of CAP compared with erythromycin and amoxicillin [31, 32]. The most common side-effects involve the gastrointestinal tract, while elevations in liver enzymes and cholestatic hepatitis are rarely reported [33, 34]. In 2013, the US Food and Drug Administration (FDA) warned about QT interval prolongation and the increased risk of cardiac arrhythmias and torsades de pointes associated with azithromycin. Although cardiac toxicity was not confirmed in all studies, caution should be used in patients using antiarrhythmics, patients with existing QT interval prolongation and the elderly [35, 36].

Clarithromycin is active at low concentrations against erythromycin-sensitive Gram-positive pathogens implicated in respiratory infections [37]. Clarithromycin presents a rapid absorption with peak serum concentrations comparable to those of azithromycin [38]. Clarithromycin is metabolised by the liver and has a relatively long half-life, allowing twice-daily administration. Dose adjustments are required for a creatinine clearance of $<30\ mL{\cdot}min^{-1}$ [39]. Clarithromycin 500 mg every 12 h has demonstrated good activity in the treatment of LRTIs [37].

Among other macrolides, roxithromycin showed equivalent cure rates compared with azithromycin in the treatment of CAP [40].

Tetracyclines: doxycycline

Doxycycline shows a bioavailability of >80% with higher absorption and lipid solubility compared with earlier drugs (*e.g.* tetracycline) [41]. Peak concentrations are achieved in 2–3 h and the elimination half-life ranges from 12 to 25 h. Doxycycline is eliminated unchanged by both the renal and biliary routes. In patients with chronic renal failure, the serum half-life of doxycycline is not greatly increased, peak plasma concentration (C_{max}) is unchanged and dose modification is usually not needed [41].

Oral doxycycline represents an option for the treatment of LRTIs due to its favourable pharmacokinetics and efficacy against ampicillin-resistant strains of *H. influenzae* and β-lactamase-producing *M. catarrhalis* [16, 42].

Respiratory fluoroquinolones: levofloxacin and moxifloxacin

Ciprofloxacin was found to show limited activity against *S. pneumoniae* and caused the rapid emergence of resistance [43]. In the late 1990s, newer molecules, the "respiratory fluoroquinolones", including levofloxacin, gatifloxacin, gemifloxacin and moxifloxacin, became available for the treatment of pneumonia [44]. The characteristics of these compounds included a broad spectrum of activity, excellent bioavailability and long half-lives, allowing once-daily administration. Furthermore, drug–drug interactions are usually minor, although all new fluoroquinolones react with metal ions and should be administered at least 2 h apart from antacids [45]. While levofloxacin and moxifloxacin are usually well tolerated and used extensively in CAP, gemifloxacin and gatifloxacin have shown significant adverse events such as hypersensitivity and glucose alterations, respectively [46]. Limited emergence of resistance to the new respiratory fluoroquinolones has been registered among pathogens involved in CAP [47].

Levofloxacin inhibits specific bacterial targets that are critical for DNA replication, such as topoisomerase IV in Gram-positive bacteria and topoisomerase II (DNA gyrase) in Gram-negative bacteria [48]. Levofloxacin is highly active against *S. pneumoniae* (MIC_{90} 1 $mg{\cdot}L^{-1}$ for penicillin-resistant strains) and against atypical organisms (MIC_{90} $\leqslant$2 $mg{\cdot}L^{-1}$) [49, 50]. Levofloxacin MIC_{90} varied from 0.25 to 4.0 $mg{\cdot}L^{-1}$ for MSSA [51]. Levofloxacin activity is limited against *Pseudomonas aeruginosa*, ESBL-producing *Klebsiella pneumoniae* and MRSA [52]. Levofloxacin is available as *i.v.* and oral formulations, with a bioavailability of 99% [53]. After oral administration, levofloxacin is absorbed rapidly, reaching its C_{max} in 2 h [53, 54], and is widely distributed in the lungs, epithelial lining fluid and alveolar macrophages [55, 56]. Levofloxacin is eliminated mainly through the kidneys, with a mean elimination half-life of 8 h, but significant increases were shown for a creatinine clearance of <50 $mL{\cdot}min^{-1}$, requiring dosage adjustment to avoid drug accumulation [53, 54]. Noninferiority of short (750 mg once daily for 5 days) *versus* long (500 mg once daily for 10 days) courses of *i.v.* or oral levofloxacin was demonstrated in patients with mild to severe CAP [54]. Short courses appeared to be linked to a higher early resolution of symptoms and high efficacy in patients with severe CAP [55]. Levofloxacin administered in 750 or 500 mg regimens is generally well tolerated [56, 57]. The most common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, headache, photosensitivity reactions and *Clostridium difficile* infection [58]. Caution is required when levofloxacin is administration simultaneously with drugs that can prolong the QT interval. An increased risk of severe tendon disorders in the elderly is also reported [59, 60].

Moxifloxacin is characterised by enhanced staphylococcal activity and reduced propensity to resistance and phototoxicity due to the presence of a C-8 methoxy group [61]. Moxifloxacin has potent bactericidal activity against intracellular and extracellular respiratory pathogens, including β-lactamase-producing *H. influenzae*, *M. catarrhalis* (MIC_{90} 0.03–0.25 $mg{\cdot}L^{-1}$) and anaerobes [62]. Against *S. pneumoniae*, moxifloxacin demonstrated 8-fold greater activity than levofloxacin [63]. While good activity has been shown against MSSA, higher MICs were reported for MRSA [64]. The terminal elimination half-life is 12 h, supporting once-daily dosing [65, 66]. Similar to levofloxacin, moxifloxacin has low protein affinity (48%) and is characterised by high penetration in respiratory tract tissues [65, 66]. Although moxifloxacin is excreted by the hepatic and renal routes, renal impairment does not significantly affect its oral clearance [67]. A prospective RCT demonstrated that monotherapy with moxifloxacin 400 mg once daily was noninferior to

 https://doi.org/10.1183/2312508X.10004316

treatment with ceftriaxone plus levofloxacin combination therapy in hospitalised patients with CAP [68]. Moxifloxacin appeared to be well tolerated in a study collecting adverse effects from clinical trials and post-marketing studies from over 50 000 patients. Gastrointestinal disturbances were the most common adverse drug reactions [69]. Various studies, however, have highlighted a correlation between fluoroquinolone use and *C. difficile*-associated diarrhoea [70–72].

Recommendations for the treatment of pulmonary infections

Various recommendations have been published for the management of LRTIs, and in particular for CAP [73–76]. Although coverage of *S. pneumoniae* and atypical pathogens using the combination of a β-lactam (*e.g.* an aminopenicillin) and a macrolide or a respiratory fluoroquinolone is often used in clinical practice, a clear outcome benefit of dual therapy has not been confirmed in all studies [77, 78]. A recent meta-analysis comparing combination therapy *versus* monotherapy concluded that the initial first-line antibiotic therapy should consist of a β-lactam plus a macrolide, or fluoroquinolone monotherapy in severe CAP requiring hospitalisation [13]. Figure 1 summarises the indications for monotherapy or combination therapy for CAP according to the American Thoracic Society/Infectious Diseases Society of America and the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases recommendations [73, 74].

Treatment of HAP

In areas with low rates of antimicrobial resistance and limited occurrence of MRSA infections, β-lactams (*e.g.* penicillins with or without β-lactamase inhibitors) are often used in clinical practice. The management of HAP, however, is currently affected in various countries by the increase in antimicrobial resistance, especially among Gram-negative bacteria. Pulmonary infections caused by ESBL-producing *Enterobacteriaceae*, MDR *Acinetobacter* spp. and *P. aeruginosa* have been documented in various areas of the world [79]. Antimicrobial resistance can cause delays in the onset of an adequate therapy and is associated with increased mortality, length of hospital stay and healthcare costs [80]. Current recommendations identify the risk of difficult-to-treat pathogens as causative agents of HAP as a key point and acknowledge the importance of local antibiograms generated by each hospital to guide treatment [15].

Treatment of pneumonia due to MRSA

MRSA represents a frequently isolated pathogen in the hospital setting and is frequently isolated in HAP, especially in ICUs [81]. Although vancomycin is still considered the first-line treatment in MRSA pneumonia, its role as a gold standard has been questioned due to the availability of therapeutic options with more favourable characteristics. Limitations in the use of vancomycin include low intrapulmonary penetration, a suboptimal clinical response for strains showing MICs >1 $mg \cdot L^{-1}$ and the need for therapeutic drug monitoring in order to achieve adequate plasma concentrations [82–84]. Linezolid, the first identified member of the oxazolidinone family, is characterised by excellent lung penetration and oral availability, and has been associated with better outcomes compared with vancomycin in the treatment of HAP due to MRSA [85]. Both vancomycin and linezolid are currently recommended for the treatment of VAP when MRSA is suspected (table 1) [15].

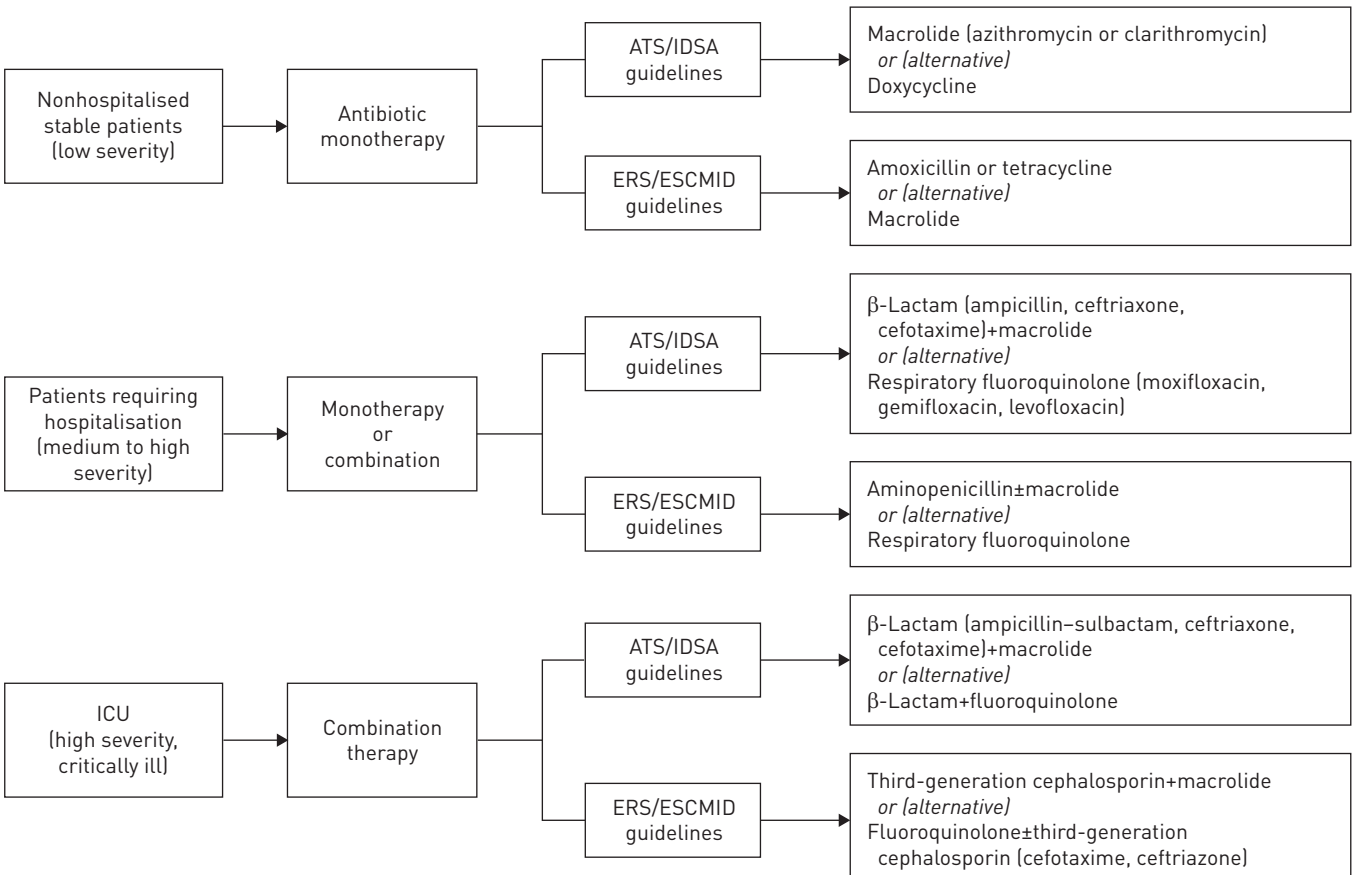

Figure 1. Recommended empirical therapy for pulmonary infections in adults according to the setting and severity of presentation [73, 74]. ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America; ERS: European Respiratory Society; ESCMID: European Society for Clinical Microbiology and Infectious Diseases.

https://doi.org/10.1183/2312508X.10004316

Table 1. Recommended empirical regimens for hospital-acquired infections taking into account the risk factors for MDR Gram-negative organisms and MRSA

Risk factors	Pathogen	Empirical therapy	Recommended regimen(s)
Noncritically ill patients; no risk factors for MRSA	MSSA[#], non-MDR Gram-negative pathogens	*Staphylococcus aureus* coverage recommended	Piperacillin–tazobactam 4.5 g *i.v.* every 6 h *or* Cefepime 2 g *i.v.* every 8 h *or* Levofloxacin 750 mg *i.v.* daily *or* Imipenem 500 mg *i.v.* every 6 h or meropenem 1 g *i.v.* every 8 h
Noncritically ill patients; *i.v.* antibiotic treatment <90 days; unit where MRSA prevalence is >20% or not known; prior MRSA detection	MRSA, resistant Gram-negative pathogens possible	One antipseudomonal agent recommended	Piperacillin–tazobactam *or* Cefepime or ceftazidime 2 g *i.v.* every 8 h *or* Levofloxacin or ciprofloxacin 400 mg *i.v.* every 8 h *or* Imipenem or meropenem *or* Aztreonam 2 g *i.v.* every 8 h *plus* Vancomycin 15 mg·kg^{-1} *i.v.* every 8–12 h[¶] *or* Linezolid 600 mg *i.v.* every 12 h

Continued

Table 1. Continued

Risk factors	Pathogen	Empirical therapy	Recommended regimen(s)
Critically ill patients; receipt of *i.v.* antibiotics <90 days	Increased risk of mortality and MDR *Pseudomonas aeruginosa* or other Gram-negative pathogens	Association of two antipseudomonal antibiotics recommended (±MRSA coverage)	Piperacillin–tazobactam *or* Cefepime or ceftazidime *or* Levofloxacin or ciprofloxacin *or* Imipenem or meropenem 1 g *i.v.* every 8 h *or* Amikacin 15–20 mg·kg^{-1} *i.v.* daily or gentamicin 5–7 mg·kg^{-1} *i.v.* daily or tobramycin 5–7 mg·kg^{-1} *i.v.* daily *or* Aztreonam

[#]: oxacillin, nafcillin and cefazolin are preferred regimens for the treatment of proven MSSA but are not recommended for empirical therapy; [¶]: loading dose 25–30 mg·kg^{-1}×1; target is 15–20 mg·mL^{-1} trough level. Information from [15].

https://doi.org/10.1183/2312508X.10004316

Glycopeptides: vancomycin

Vancomycin is not absorbed orally and is primarily renally eliminated [86]. Protein binding ranges from 10% to 50%, with a volume of distribution of 0.4–1 $L \cdot kg^{-1}$ [87]. Vancomycin penetration in the lung is variable. Studies have reported concentrations of 41% in lung tissue and 52% in the epithelial lining fluid [82, 88]. In critically ill patients, penetration of vancomycin into the epithelial lining fluid ranged from 0 to 8.1 $mg \cdot L^{-1}$, showing an overall blood/epithelial lining fluid penetration ratio of 6/1 [89]. A study investigating optimal pharmacokinetic/pharmacodynamic parameters associated with clinical success established that an AUC/MIC ratio of $\geqslant$350 was necessary in the treatment of staphylococcal pneumonia [90]. To maximise the likelihood of achieving an adequate AUC, increased dosing to maintain vancomycin trough levels between 15 and 20 $mg \cdot L^{-1}$ in serious MRSA infections is suggested [91, 92]. This dosing schedule, along with other factors (*i.e.* concomitant nephrotoxic agents, patient comorbidities and therapy duration), has been correlated with nephrotoxicity [93]. Other adverse effects associated with vancomycin use include aminotransferase elevations, neutropenia and infusion reactions [94, 95].

Oxazolidinones: linezolid

Linezolid binds to the bacterial ribosome 50S subunit and interferes with protein synthesis [96]. Linezolid has demonstrated excellent activity against most Gram-positive bacteria involved in respiratory infections, including MRSA [97]. Linezolid is available in *i.v.* and oral formulations, and exhibits linear pharmacokinetics, with oral bioavailability close to 100% when administered as 600 mg every 12 h. Linezolid therapy is characterised by the possibility of de-escalation from *i.v.* to oral dosing without dose adjustments [98]. After oral doses of 600 mg, C_{max} is reached in 30 min to 2 h [99]. Linezolid plasma protein binding is low (31%), while its volume of distribution approximates to the total body water content (40–50 L). Plasma elimination half-life was reported to be between 3.4 and 7.4 h. Around 65% of linezolid is metabolised by nonrenal mechanisms [100]. Although no drug adjustments are necessary for patients with renal impairment or mild to moderate liver disease [100], it is recommended that linezolid is used with caution in patients with severe renal insufficiency. Initial studies confirmed excellent concentrations of linezolid in the epithelial lining fluid [101]. Subsequently, a study in critically ill patients with VAP showed mean peak and trough concentrations of 17.7 and 2.4 $mg \cdot L^{-1}$ in plasma and 14.4 and 2.6 $mg \cdot L^{-1}$ in epithelial lining fluid, respectively, and a mean penetration in the epithelial lining fluid of 100% [102]. The linezolid spectrum of activity and the excellent pharmacokinetics of linezolid in the lung support its role in MRSA pneumonia. Use of linezolid, however, has been associated with the onset of various adverse effects including nausea, headache, peripheral and optic neuropathy, lactic acidosis and myelosuppression (especially thrombocytopenia). The majority of the effects were reported during prolonged regimens (>14 days) and in patients with renal impairment [103, 104]. Linezolid is also a reversible monoamine oxidase inhibitor and can interact with selective serotonin reuptake inhibitors [105].

Treatment of MDR pathogens causing HAP

Treatment of MDR Gram-negative bacteria, especially carbapenem-resistant strains, represents one of the biggest challenges for clinicians managing severe infections. A few observational studies have reported better outcomes for colistin-based regimens compared

with monotherapy in the treatment of carbapenem-resistant infections [106–108]. Limitations in the use of colistin, however, include unclear pharmacokinetic/pharmacodynamic parameters and dosing regimen, poor lung penetration and renal toxicity [109]. Although the combination of *i.v.* and nebulised colistin is suggested in severe infections, large studies analysing the benefit of this association have not yet been published [109].

Other antimicrobials used in the treatment of pneumonia include aztreonam, characterised by excellent tolerability but limited by a narrow antimicrobial spectrum including only Gram-negative bacteria, and aminoglycosides. Lung penetration of aminoglycosides, however, is scarce [110]. Gentamicin, amikacin and tobramycin are used in combination with other antimicrobials for the treatment of HAP caused by MDR pathogens [15].

Table 1 summarises the antimicrobial regimens for the treatment of HAP according to the recent Infectious Diseases Society of America recommendations [15]. For HAP and VAP, recommended regimens take into account patient risk factors, hospital epidemiology and local antimicrobial resistance trends. Recommendations for empirical treatment of MDR Gram-negative pathogens, however, are generally supported by low-quality evidence due to the lack of well-designed trials and the paucity of data on the use of new antimicrobials in real-world studies.

New antimicrobials for the treatment of pulmonary infections

A number of new antimicrobials with activity against respiratory pathogens including MDR bacteria, especially MRSA, have recently been approved and other agents are under investigation. Although the efficacy of many new compounds still needs to be confirmed, promising features include a broad spectrum of activity, limited risk of antimicrobial resistance, availability of *i.v.* and oral formulations, and a favourable safety profile. Table 2 summarises the characteristics and current approval status of new antimicrobials that have been studied for the treatment of pulmonary infections.

Cephalosporins

Ceftaroline and ceftobiprole are new fifth-generation cephalosporins with high activity against MRSA due to their affinity for the penicillin-binding protein PBP2a [111].

The ceftaroline spectrum of activity includes resistant Gram-positive bacteria (including MRSA with reduced susceptibility to vancomycin and penicillin-resistant *S. pneumoniae*) and most Gram-negative bacteria, with the exception of ESBL-producing and carbapenem-resistant *Enterobacteriaceae* [112]. The association of ceftaroline with avibactam, a novel non-β-lactam β-lactamase inhibitor, significantly expands the spectrum of activity of ceftaroline and includes ESBL-, AmpC- and *K. pneumoniae* carbapenemase (KPC)-producing bacteria, representing an interesting future option for respiratory infections [113]. Ceftaroline received FDA approval in 2010 for the treatment of skin and soft tissue infections and CAP. The efficacy of ceftaroline (600 mg every 12 h) in the treatment of CAP has been evaluated in two randomised trials showing clinical cure rates in 80% of patients along with a favourable safety profile [114, 115]. Although administration of increased doses of ceftaroline (600 mg every 8 h) has been associated with improved clinical outcomes in MRSA infections, numerous adverse events (*e.g.* neutropenia) have been reported, especially for prolonged treatments [116, 117].

 https://doi.org/10.1183/2312508X.10004316

Table 2. New antimicrobials that can be used for the treatment of community- or hospital-acquired infections

Antimicrobial class	Name	MRSA and MDR Gram-negative activity	Dosage and administration	Status for pulmonary infections
Cephalosporin	Ceftaroline	MRSA; no ESBL producers or *Pseudomonas*	600 mg every 12 h *i.v.*	Approved for CAP
Cephalosporin	Ceftobiprole	MRSA; *Pseudomonas* but not ESBL producers	500 mg every 12 h *i.v.*	Approved for CAP and HAP (Europe)
Cephalosporin/ β-lactamase inhibitor	Ceftazidime–avibactam	Gram-negatives including ESBL producers and KPC-producing *Klebsiella pneumoniae*, AmpC cephalosporinases and OXA-48 (no metallo-β-lactamase)	2.5 g every 8 h *i.v.*	Approved for cIAIs and cUTIs; phase III for HAP and VAP
Cephalosporin/ β-lactamase inhibitor	Ceftolozane–tazobactam	Gram-negatives including ESBL producers and MDR *Pseudomonas*	1.5 g every 8 h *i.v.*	Approved for cIAIs and cUTIs; phase III trial for VAP due to *P. aeruginosa* (3 g every 8 h)
Fluoroketolide	Solithromycin	No MDR Gram-negative, no MRSA	400 mg once daily	Phase III trials for CAP
Lipoglycopeptide	Telavancin	MRSA	10 $mg \cdot kg^{-1}$ every 24 h *i.v.*	Approved
Oxazolidinone	Tedizolid	MRSA	200 mg every 24 h *i.v.* and oral	Investigational (approved for SSTIs)
Fluoroquinolone	Delafloxacin	MRSA, *Pseudomonas* but not ESBL producers	300 mg every 12 h *i.v.* and oral	Phase II in CAP
Fluorocycline	Eravacycline	MRSA, MDR Gram-negative, no *Pseudomonas*	Under investigation; *i.v.*	Investigational

KPC: *Klebsiella pneumoniae* carbapenemase; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; SSTI: skin and soft tissue infections.

Ceftobiprole is currently approved for clinical use in Europe and has been studied in the treatment of CAP requiring hospitalisation, HAP and VAP [118, 119]. While ceftobiprole noninferiority *versus* ceftriaxone (with or without linezolid) and ceftazidime plus linezolid was demonstrated in CAP and HAP, low response rates (23.1%) were found in patients with VAP, limiting its use in this indication.

Ceftazidime–avibactam has been approved by the FDA for the treatment of complicated intra-abdominal and complicated urinary tract infections. Ceftazidime–avibactam has a broad spectrum of activity, including ESBL-, AmpC- and KPC-producing Gram-negative

pathogens [120]. Due to its good penetration into lung tissue, ceftazidime–avibactam represents a good option for the treatment of pulmonary infections caused by carbapenem-resistant Gram-negative bacteria [121, 122]. A recently completed phase III study showed noninferiority of ceftazidime–avibactam compared with meropenem for the treatment of HAP and VAP [123].

Ceftolozane–tazobactam is the association of a new antipseudomonal cephalosporin with tazobactam, a well-known β-lactamase inhibitor. Ceftolozane possesses a potent antipseudomonal activity and is not affected by mechanisms of resistance that are typical of *P. aeruginosa*, such as changes in porin permeability and upregulation of efflux pumps [124]. The association of ceftolozane with tazobactam broadens the spectrum of activity of ceftolozane, especially against class A ESBL-producing *Enterobacteriaceae* [125]. Ceftolozane–tazobactam is currently approved for the treatment of complicated intra-abdominal and complicated urinary tract infections. Although ceftolozane–tazobactam has shown good epithelial lining fluid penetration, pharmacokinetic/pharmacodynamic studies have suggested that an increased dosage might be necessary for the treatment of pneumonia in order to achieve an optimal response [126, 127]. A phase III trial to assess the safety and efficacy of high-dose ceftolozane–tazobactam compared with meropenem for the treatment of VAP due to *P. aeruginosa* is currently ongoing (ClinicalTrials.gov, trial number NCT02070757) (table 2).

Fluoroketolides

Solithromycin is a fourth-generation macrolide antibiotic and the first fluoroketolide within the macrolide class. Similar to other ketolides, it binds to bacterial 23S ribosomal RNA and interacts with domains V and II and with a third site of interaction between the fluorine at position C-2 and the peptide in the exit tunnel. Multiple interacting sites are involved in its low resistance rates and improved activity against macrolide-resistant isolates of *S. pneumoniae* [128].

Solithromycin has activity against the most common respiratory pathogens and atypical bacterial pathogens, including *Legionella pneumophila*, shows bactericidal activity against most isolates of *S. pneumoniae* and *H. influenza*, and demonstrated a low potential for *C. difficile* selection [129].

Solithromycin is available in oral and *i.v.* formulations. When administered as 400 mg once daily, solithromycin had a bioavailability of ~67% and a plasma half-life of 10 h [128]. Solithromycin is excreted primarily by the liver and no dose adjustment is needed in patients with hepatic impairment. In patients with severe renal impairment, a dose reduction is recommended [128]. The drug–drug interaction profile of solithromycin is consistent with that of previously approved macrolides [128].

The efficacy and safety of solithromycin in the treatment of CAP were established in two large phase III studies showing noninferiority to moxifloxacin [130, 131]. Although a higher incidence of infusion site reactions was demonstrated in the solithromycin arm compared with moxifloxacin, other adverse effects were similar in the two arms. Diarrhoea (4.3%), headache (4%) and nausea (3.4%) were the most frequently reported adverse events [131].

 https://doi.org/10.1183/2312508X.10004316

Lipoglycopeptides

Telavancin belongs to the lipoglycopeptides and is characterised by a broad spectrum of activity against Gram-positive pathogens involved in pulmonary infections, including MRSA [132]. Telavancin acts by disrupting the bacterial membrane function and inhibiting bacterial wall synthesis *via* transglycosylation and transpeptidation, using a unique dual mechanism of action [133]. Due to its good penetration into the epithelial lining fluid, telavancin has been studied in the treatment of HAP and was demonstrated to be noninferior compared with vancomycin [134, 135]. However, studies analysing telavancin safety in the treatment of HAP showed higher rates of nephrotoxicity along with increased serious adverse events and mortality among patients with moderate to severe renal impairment compared with vancomycin [136]. Due to the adverse effects of telavancin in patients with renal impairment, its use is restricted to patients with normal renal function, and it is recommended in MRSA infections only where alternative options are not suitable [137, 138].

Oxazolidinones

Among oxazolidinones, tedizolid is currently approved for the treatment of acute bacterial skin and soft tissue infections. The efficacy of tedizolid for the treatment of MRSA pneumonia has been demonstrated in murine models, where tedizolid achieved higher epithelial lining fluid penetration compared with linezolid [139, 140]. Recent pharmacokinetic/pharmacodynamic studies confirmed high epithelial lining fluid concentrations of tedizolid in healthy volunteers after 200 mg of tedizolid administered orally, supporting its potential role in the treatment of pneumonia [141].

Fluoroquinolones

Delafloxacin is a fluoroquinolone antibiotic available as an oral formulation with high activity against respiratory pathogens such as MRSA, *S. pneumoniae* (including levofloxacin-resistant strains), *H. influenzae* and *M. catarrhalis* [142]. A phase II study investigated the efficacy of delafloxacin in the treatment of CAP and acute bacterial exacerbation of chronic bronchitis at different dosages (100–400 mg every 24 h), showing clinical and bacteriological response rates of between 80% and 88% [143].

Fluorocyclines

Eravacycline is a novel fluorocycline that is not influenced by the mechanisms that usually confer resistance to tetracyclines, such as efflux pumps and ribosomal protection proteins [144]. Eravacycline achieves concentrations 6- and 50-fold higher in the epithelial lining fluid and in alveolar macrophages than in plasma, respectively, and was shown to be as effective as linezolid and more effective than vancomycin in MRSA mouse lung infection models [145, 146]. Eravacycline has a broad spectrum of activity, including MRSA, penicillin-resistant and macrolide-resistant *S. pneumoniae* and MDR Gram-negative pathogens [147]. These data, together with the availability of an oral formulation, make eravacycline an attractive option for the treatment of respiratory infections.

Table 3. Characteristics of antimicrobials that are currently commonly used in the treatment of respiratory infections

Class	Spectrum	Lung penetration	Sequential therapy (*i.v.* to oral)
Penicillins	No MRSA, no ESBL or MDR *Pseudomonas*	Good	No[#]
Macrolides	A few MRSA, no ESBL or MDR *Pseudomonas*	Moderate	Yes
Tetracyclines	Some MRSA, no ESBL or MDR *Pseudomonas*	Moderate	Yes
Fluoroquinolones	A few MRSA, no ESBL or MDR *Pseudomonas*	Very good	Yes
Cephalosporins	No MRSA (except ceftaroline and ceftobiprole), no ESBL or MDR *Pseudomonas*	Good	No
Carbapenems	No MRSA, includes ESBL and MDR *Pseudomonas*	Good	No
Oxazolidinones (linezolid)	Includes MRSA, no Gram-negatives	Excellent	Yes
Glycopeptides (vancomycin)	Includes MRSA, no Gram-negatives	Low	No
Aminoglycosides	No MRSA[¶], in combination therapy for MDR Gram-negatives	Low	No

[#]: possible for amoxicillin–clavulanate; [¶]: MRSA susceptibility for gentamicin is often reported, but it is rarely used as monotherapy for the treatment of MRSA infections.

Conclusions

LRTIs represent frequent conditions burdened by high morbidity and mortality, and require a timely and appropriate antimicrobial therapy. Challenges in the treatment of respiratory infections encountered in clinical practice are the frequent absence of microbial diagnosis to guide antimicrobial choice and, in some areas, an increased rate of antimicrobial resistance among pathogens that are usually involved in these infections, especially in the nosocomial setting. A short course of antimicrobials should be favoured, where possible, to reduce resistance selection; de-escalation therapy should also be pursued to reduce length of hospital stay and healthcare costs. Various classes of antimicrobials are currently used in the treatment of LRTIs. A summary of their characteristics, including molecules used in severe forms and for MDR pathogens, is shown in table 3. Limitations in the use of antimicrobials, however, include variable penetration in the lung tissue, availability only as an *i.v.* formulation and a limited spectrum of action. To overcome these issues and to face the emerging increase in resistance to antimicrobials, new molecules have been developed. Large prospective real-world studies investigating the efficacy of new compounds in the treatment of LRTIs are required.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10004316

Antibiotic resistance in pulmonary infections: mechanisms and epidemiology

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Bacterial resistance to antimicrobials is a natural process driven by selective pressure. It is caused by mutational alteration of the genetic information or by incorporation of mobile genetic elements carrying resistance genes. Reduced influx or increased efflux of the antimicrobials often leads to multidrug resistance, whereas mutations in genes encoding antibiotic targets are generally related to resistance to specific antimicrobial classes. In this chapter, we give an overview of the most common resistance mechanisms found in bacterial pathogens of LRTIs.

Cite as: Makarewicz O, Klinger-Strobel M, Ehricht R, *et al*. Antibiotic resistance in pulmonary infections: mechanisms and epidemiology. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 21–43 [https://doi.org/10.1183/2312508X.10004416].

LRTIs can be generally divided into three types: 1) community-acquired LRTIs (*e.g.* CAP, acute exacerbations of COPD (AE-COPD) and exacerbations in non-cystic fibrosis (CF) bronchiectasis), 2) HAP (including VAP) and 3) pneumonia in immunocompromised patients (the latter is not discussed in this chapter). Each type of LRTI is related to the characteristic aetiology of the pathogens. Effective empiric antimicrobial therapy of LRTIs and pneumonia has increasingly been threatened by the spread of (multidrug) resistant pathogens in the recent past. Resistance to antimicrobials can be either intrinsic or acquired. Acquired antimicrobial resistance is associated with mechanisms that are rather similar in many bacterial species because they are related to conserved processes (*e.g.* replication, translation and efflux). In contrast, intrinsic resistance is associated with morphological properties (*e.g.* the lack of the cell wall in *Mycoplasma* spp. or natural impermeability of the outer membrane in *Pseudomonas aeruginosa*) and the intracellular life cycle (*e.g.* in *Chlamydia*, *Coxiella* and *Legionella* spp.). Phenotypic

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

antimicrobial resistances are also associated with changes of lifestyle (*e.g.* intracellular escape (*Staphylococcus aureus*) or biofilm formation (*P. aeruginosa* and *Staphylococcus epidermidis*)).

We first give an overview of the general mechanisms of antimicrobial resistance development and the definition of resistance. Specific resistance mechanisms and the epidemiology of antimicrobial resistance are then discussed with respect to the main pathogens of LRTIs.

Antimicrobial resistance

Genotypic drug resistance

The emergence of any resistance is a natural evolutionary process of organisms that is driven by one or a multitude of selective pressures. One main mechanism of resistance development is mutagenesis, which allows the changes to be passed on to the following generations and stable resistance to be established. For example, the spontaneous mutation frequency in *Escherichia coli* has been determined to be 5.4×10^{-10} bp per replication [1], equivalent to approximately one mutation per 10 000 genomes. Thus, in a habitat such as BAL fluid with 10^4 cells·mL^{-1} [2], one can expect at least one spontaneous mutant per millilitre, with at least one mutation in any DNA region. Of course, the probability that a mutation occurring in a specific gene leads to detectable changes in the phenotype is lower by magnitudes, but sequence "hotspots" exist that contain favoured sequences where mutations occur at higher frequencies [3, 4]. Therefore, mutation frequencies vary depending on many factors, such as base sequence, gene location and organism, and can be increased up to 10^4-fold by stress factors, such as exposure to antimicrobials or mutagens [5]. Looking at resistance to a specific antimicrobial compound, resistance rates of 1 per 10^9 to 1 per 10^{10} cells have been described for clinical isolates (*e.g.* for *Streptococcus pneumoniae*), but were 100-fold higher for mutator strains that in general exhibit higher mutation frequencies due to defects in the key replication or repair mechanisms, such as topoisomerases and DNA gyrases [6].

In addition to single base substitutions, other processes contribute to the emergence of resistance in microorganisms. Bacteria are able to exchange their genetic material by horizontal gene transfer (*e.g.* conjugation of plasmids, transduction *via* phages and uptake of free DNA) even among different bacterial species, allowing rapid accumulation and spread of countless different resistance variations at a relatively high evolutionary pace.

Resistance against antimicrobials is mediated *via* four different general mechanisms [7] and often one mechanism mediates resistance to various even nonrelated drugs, or more than one mechanism mediates resistance to one drug, in a single isolate: 1) alteration in the target site lowering the affinity to the antimicrobial or a new target site with low affinity to the antimicrobial; 2) enzymatic modification or hydrolysis of the antimicrobial; 3) increased efflux of the antimicrobial mediated by efflux pumps or the reduced influx of the antimicrobial due to decreased permeability; and 4) modification of metabolic pathways to circumvent the antibiotic effect

Breakpoints and resistance definition

As microorganisms, in particular bacteria, have short generation times (in the range of minutes and hours), an exponentially growing bacterial population can achieve high diversity, bearing various subpopulations of bacteria cells with altered genotypes and

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phenotypes, in a short period of time. Looking at the distribution of MICs of a particular drug, the major part of a population will show a normal distribution of the MIC representing the wild-type population, but some bacteria disseminate from the normal distribution. The epidemiological cut-off (ECOFF) value indicates the upper border that separates the wild-type microorganisms without a resistance mechanism (normal distribution) from the non-wild-type microorganisms with an acquired mechanism of resistance (increased MICs). The clinical MIC breakpoints, which often do not comply with the ECOFF values, differentiate between microorganisms of a particular species that are clinically susceptible, intermediate (there is not always this category) or resistant against a specific antibiotic (figure 1). In Europe, breakpoints for phenotypic antimicrobial susceptibility testing are set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in cooperation with national antimicrobial susceptibility testing committees. A clinical breakpoint is not given if a bacterial species is deemed intrinsically resistant to an antimicrobial agent. Relevant factors in setting breakpoints for antimicrobial agents include clinical indications, evaluation of efficacy in experimental settings and clinical studies to derive pharmacodynamics targets, such as the ratio of the unbound to the MIC (*f*AUC/MIC) or the time over the MIC (*fT*>MIC) required for efficacy, the pharmacokinetic properties of the agent, Monte Carlo simulations to estimate exposures of the antimicrobial agent in the target patient population, standard and maximum dosing regimens, and MIC distributions of target organisms.

Two clinical breakpoints are set for some antimicrobials and bacterial species (*e.g.* penicillin resistance in *S. pneumoniae*), depending on the clinical indication and dosing (figure 1).

Phenotypic antimicrobial tolerance

In addition to genetic resistance, microorganisms possess different possibilities to escape antimicrobial treatment by phenotypic tolerance to antimicrobials that is often worded ambiguously as "phenotypic resistance". The primary mechanism is formation of biofilms (*e.g. P. aeruginosa* forms biofilms in lungs of CF patients). Biofilms are microbial communities embedded in a self-produced matrix, which is composed of oligosaccharides, proteins and nucleic acids. Biofilms can be formed on almost all organic and inorganic

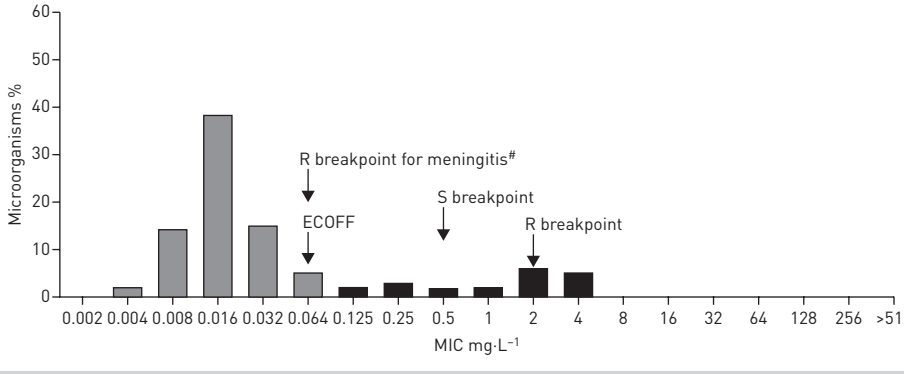

Figure 1. International distribution of benzylpenicillin MICs in *Streptococcus pneumoniae*. The distribution is based on 37 742 observations. Epidemiological cut-off (ECOFF) 0.064 mg·L^{-1}, susceptibility (S) ⩽0.5 mg·L^{-1}, resistance (R) ⩾2 mg·L^{-1}. #: in the case of meningitis, resistance is assumed at MIC >0.064 mg·L^{-1}. Data from the European Committee on Antimicrobial Susceptibility Testing MIC distribution website (www.eucast.org).

surfaces, and are poorly eradicable by common drug treatments because the biofilm matrix confers robust tolerance to antibiotics and protects the bacteria against the immune response. It has been discussed that subinhibitory antibiotic concentrations might even induce biofilm formation [8]. The minimum biofilm-eliminating concentration of an antibacterial agent can be 1000-fold higher than the MIC determined using planktonic-cultured cells, which is not considered in current routine diagnostics [9]. One reason for the drug tolerance is the reduced metabolic activity of the embedded microorganisms. Most antibiotics target metabolic processes, but microbes in deeper layers of a biofilm exhibit nearly no metabolic activity due to reduced oxygen and nutrient concentrations. Furthermore, reduced drug permeability (*e.g.* of aminoglycosides) into the biofilm due to decreased penetration of charged antimicrobials or sequestration by matrix polymers as well as enrichment of extracellular antibiotic-hydrolysing enzymes (*e.g.* β-lactamases) in the matrix render the antimicrobials ineffective [10].

Another phenotype that exhibits resistance beyond the classical resistance mechanisms is represented by so-called small colony variants (SCVs), which are a common phenomenon in *S. aureus*, for example [11, 12]. SCVs are slow-growing variants of bacteria that exhibit atypical colony morphologies and unusual biochemical features; therefore, these often remain unidentified during routine diagnostic tests. SCVs display reduced expression of virulence factors, but increased expression of adhesins. This allows invasion of the host cells and persistence therein for several weeks, thereby escaping the host response and antibiotic treatment [13]. The altered bacterial phenotype is not stable in clinical isolates and converts to the wild-type under promotive conditions, causing recurrent infections.

It must also be noted that due to the lack of a cell wall, *Mycoplasma* spp. are innately resistant to β-lactams and glycopeptides. They are also intrinsically resistant to colistin and cotrimoxazole (trimethoprim–sulfamethoxazole) [14].

Pathogens of LRTIs

Worldwide, the most abundant pathogens identified in CAP patients are *S. pneumoniae* [15], *Mycoplasma pneumoniae* [16], *Haemophilus influenzae* [17], some *Chlamydia* spp. [18], *Legionella pneumophila* [19] and the influenza virus [20]. Other relevant pathogens found at lower frequency are *S. aureus* [15], *Enterobacteriaceae* [21] and *Coxiella burnetii* [22] (figure 2, dark grey bars). Dual bacterial or dual viral infections occur in up to 14% of all cases, whereas mixed viral/bacterial infections have been described in up to 30% of all cases. The most concomitant species of influenza-associated pneumonia are *S. pneumoniae*, *H. influenzae* and *S. aureus* [20, 24].

The spectrum of pathogens identified in AE-COPD is more variable, and is strongly influenced by the lung function and vaccination status of the patient, as well as by previous antibiotic use and hospitalisation periods. Thereby, bacteria make up a minority of the exacerbations and often no pathogen can be identified [15]. In general, all of the pathogens described for CAP can be found; however, the role of atypical bacteria (*Mycoplasma*, *Chlamydia* and *Legionella*) remains unclear (figure 2, medium grey bars). Whereas *P. aeruginosa* remains rare in CAP [21], it can be found as a cause of AE-COPD in patients with advanced-stage COPD and bronchiectasis. Pathogens associated with exacerbations in non-CF bronchiectases are primarily *P. aeruginosa* and *H. influenzae* [25, 26], but *Enterobacteriaceae*, *S. aureus* and NTM have also been identified [15] (figure 2, light grey bars).

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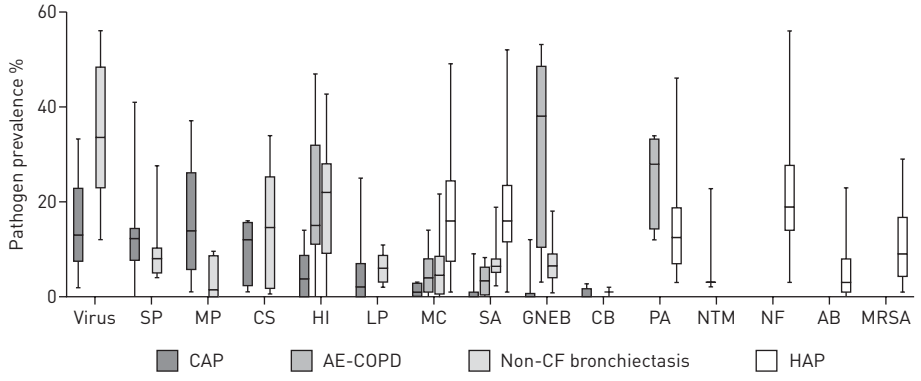

Figure 2. Prevalence of pathogens identified in different types of LRTIs. SP: *Streptococcus pneumoniae*; MP: *Mycoplasma pneumoniae*; CS: *Chlamydia* spp.; HI: *Haemophilus influenzae*; LP: *Legionella pneumophila*; MC: *Moraxella catarrhalis*; SA: *Staphylococcus aureus*; GNEB: Gram-negative enterobacteria; CB: *Coxiella burnetii*; PA: *Pseudomonas aeruginosa*; NF: *Nocardia farcinica*; AB: *Acinetobacter baumannii*; AE-COPD: acute exacerbation of COPD; CF: cystic fibrosis. Data for community-associated pneumonia (CAP, AE-COPD and non-CF bronchiectasis) from [15]; data for HAP from [23].

The spectrum of pathogens in HAP differs significantly from CAP. In general, *S. aureus*, *P. aeruginosa*, *Enterobacteriaceae* and *Acinetobacter baumannii* represent the most frequent pathogens in HAP [23] (figure 2, white bars), but the prevalence and resistance rates of the pathogens to common antibiotics may differ regionally depending on the epidemiological situation in a given country.

Resistance mechanisms

The section introduces efflux and influx as mechanisms of multidrug resistance. Both efflux and influx are often not limited to one compound. The efflux encoding genes conferring resistance to multiple drugs belong to the basic equipment of many species (intrinsic resistance), but may also be acquired (on plasmids or other genetic elements) or induced by the antimicrobial (*via* accessory genes). Resistance related to porins is usually acquired by mutation in the respective genes, which leads to altered or loss of function.

The drug (class)-specific genetic resistance determinates, which are acquired by mutations or transferable elements, are discussed in the various subsections (sorted by the antibiotic class) with a brief introduction of their mode of action for a better understanding of the underlying resistance mechanisms (for an overview, see figure 3).

Influx-related resistance and multidrug efflux

Bacteria have developed various mechanisms to reduce the intracellular concentration of toxins, such as antimicrobials. Efflux pumps transport energy-dependent (*i.e.* utilising ATP or the proton motive force of the membrane) but relatively unspecific toxins and other substances out of the cell. Thus, one efflux pump may be sufficient for a variety of antimicrobials. Efflux pumps can be divided into five groups: 1) the major facilitator superfamily (MFS), 2) the ATP-binding cassette (ABC) family, 3) the resistance–nodulation–division (RND) family, 4) the small multidrug resistance (SMR) family, and

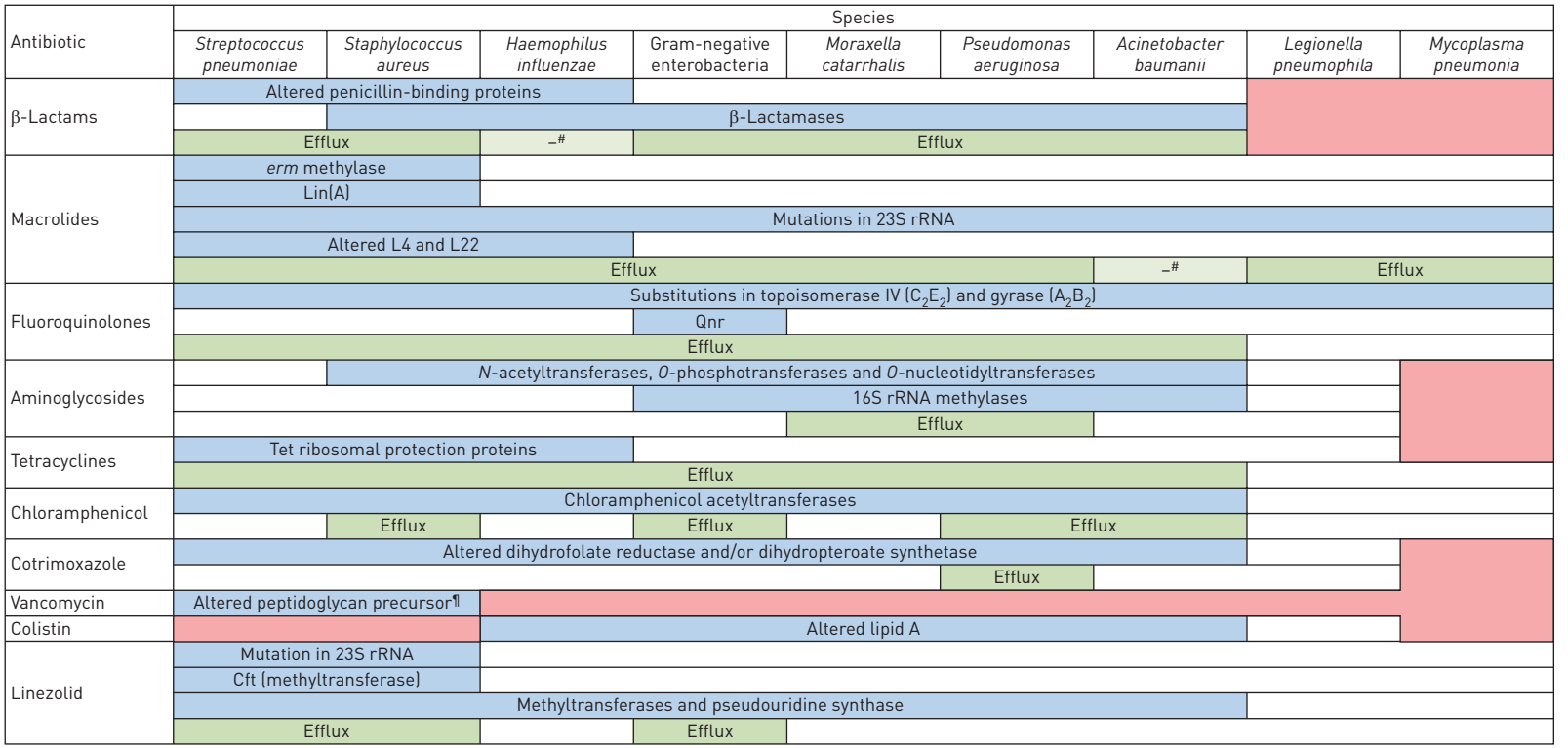

Figure 3. Acquired specific resistance mechanisms in most common pathogenic bacteria detected in LRTIs. Intrinsic tolerance/resistance is indicated by red boxes. For more details about the efflux pumps, see table 1. #: efflux of the respective antibiotic class is most probably due to the presence of efflux pump components that are homologous to those with known function in other species; ¶: *van* genes.

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Table 1. Characterisation of the efflux systems found in pathogens of LRTIs

Species	Efflux pump	Expression	Substrates
Gram-positive and atypical bacteria	Tet(K), Tet(L)	Downregulated by attenuation in absence of tetracycline	Tetracyclines
Gram-negative bacteria	Tet(A), Tet(B), Tet(C), Tet(D), Tet(E), Tet(I), Tet(Y)	Under *cis*-control *via* Tet repressor, inducible by tetracycline	Tetracyclines
Enterobacteriaceae	ArcAB–TolC	Housekeeping gene under ArcR repressor control, inducible by general stress	Fluoroquinolone, tetracycline/tigecycline, chloramphenicol, β-lactams, linezolid
	MdfA, NorE		Fluoroquinolones
	GepA		Fluoroquinolones
	CmlA		Chloramphenicol
Haemophilus influenzae	ArcAB	Housekeeping gene under ArcR repressor control, inducible by general stress	Macrolides and ketolides
Moraxella catarrhalis	ArcAB–OprM	Inducible by antibiotic exposure	Macrolides and β-lactams
Legionella pneumophila	ArcAB–TolC		Macrolides
Pseudomonas aeruginosa	MexAB–OprM	Constitutive, but under MexR repressor control	Fluoroquinolones, tetracycline/tigecycline, chloramphenicol, macrolides, β-lactams, cotrimoxazole
	MexXY–OprM	Constitutive, but under MexZ repressor control	Fluoroquinolones, tetracycline/tigecycline, chloramphenicol, aminoglycosides
	MexCD–OprJ	Inducible by disinfectants	Fluoroquinolones, macrolides, tetracycline/tigecycline, some β-lactams
	MexEF–OprN	Under positive control of MexT (might be plasmid encoded)	Fluoroquinolones, chloramphenicol, trimethoprim, various β-lactams including carbapenems, cotrimoxazole
Streptococcus pneumoniae	PmrA, PatAB		Fluoroquinolones
	Mef(A), MsrD		Macrolides
	spr1021 and spr1887		Linezolid
Staphylococcus aureus	NorA, NorB, NorC	Repression by MgrA, activation by NorG	Fluoroquinolones, tetracyclines (NorB)
	AbcA	Repression by NorG, activation by MgrA	β-Lactams
	MepA	Under MepR repression	Tigecycline, chlorhexidine
	Msr group		Macrolides, streptogramin B
	LmrS		Lincomycin, linezolid, trimethoprim, florfenicol, chloramphenicol, erythromycin, streptomycin

5) the multidrug and toxic compound extrusion (MATE) family. Additionally, impeded permeability of a compound into the periplasm or the cytoplasm may reduce the antimicrobial efficiency. The uptake of antimicrobials is generally through passive transport; thereby, charged antimicrobials (*e.g.* β-lactams and macrolides) pass through the outer membrane *via* the porins, whereas uncharged (*e.g.* fluoroquinolones), amphiphilic (*e.g.* colistin) or lipophilic antimicrobials (*e.g.* macrolides) can permeate through the membranes [27].

Tet efflux

The Tet family of MFS efflux pumps is widespread within bacteria and is associated with resistance to tetracyclines (table 1). Tet(K) and Tet(L) are commonly found in Gram-positive bacteria (including *S. pneumoniae* and *S. aureus*) and in *Mycoplasma* spp. They have been proposed to be regulated by attenuation in the absence of tetracycline. This idea is supported by a potential stem–loop messenger RNA (mRNA) structure with two alternative ribosome-binding sites [28]. The number of Tet efflux pumps in Gram-negative bacteria can vary from one (Tet(B) in *Moraxella catarrhalis*) up to seven (*e.g.* in *E. coli*) (table 1) [28]. The *tet* genes are *cis*-regulated by specific repressors that are divergently located upstream of the *tet* genes. Binding of tetracycline to a repressor changes its conformation and releases the repressor from the *tet* promoter, resulting in the expression of the Tet efflux pump [29]. In *S. aureus*, *tet*(K) expression has also been shown to be induced by doxycycline, but not by minocycline [30].

Genes encoding the Tet efflux pumps are often located on plasmids and therefore can be exchanged rapidly even between less-related species. For example, the first tetracycline-resistant *H. influenzae* isolate carrying the plasmid-encoded *tet*(B) gene was reported in 1975, most probably as a result of a conjugative transfer from *Enterobacteriaceae* or *Pseudomonadaceae*, where *tet*(B) was identified earlier [28]. Most of the Tet efflux pumps are specific for tetracycline, except for Tet(A) and Tet(B), which confer resistance to both tetracycline and minocycline.

Efflux in Gram-negative bacteria

In *E. coli* and other *Enterobacteriaceae*, the overexpression of the major RND efflux pump AcrAB–TolC is related to the increased MICs of β-lactams, fluoroquinolones, tetracyclines and tigecycline or chloramphenicol [31], whereas the MFS efflux pumps MdfA and NorE have been primarily associated with reduced susceptibility to fluoroquinolones [32], and the CmlA transporter often located on a plasmid near the *catA* gene (see the section on chloramphenicol) is specific for chloramphenicol [33]. Homologous transporters have been shown to export macrolides and ketolides in *H. influenzae* [34], as well as aminoglycosides and, to a lesser extent β-lactams, in *M. catarrhalis* [35]. The overexpression of AcrAB in both *Enterobacteriaceae* and *H. influenzae* is caused by mutations inactivating ArcR, a repressor of the *arcAB* operon. The AcrAB–TolC homologue also mediates multidrug resistance in *L. pneumophila* [36].

P. aeruginosa has a naturally low impermeability of the outer membrane and produces 12 efflux systems which confer resistance to a broad range of antibiotics. These render many antimicrobials ineffective against *P. aeruginosa.* Among the efflux pumps, overexpression of MexAB–OprM and MexXY–OprM has the highest prevalence in clinical isolates; however, overexpressed MexCD–OprJ or MexEF–OprN has also been shown to efficiently remove fluoroquinolones and other antimicrobials from the cytoplasm (table 1) [37, 38]. Furthermore, *Enterobacteriaceae* and other Gram-negatives (*P. aeruginosa*, *A. baumannii*

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and *H. influenzae*) exhibit several porins. Mutations leading to alterations of their structure or loss may additionally reduce the susceptibility to different antibiotics, such as β-lactams, tetracyclines or macrolides. In combination with other specific resistance mechanisms, modifications of efflux and influx result in highly resistant phenotypes [31].

The plasmid-borne *qepA* gene encoding an efflux pump and conferring resistance to fluoroquinolones has been identified in some *E. coli* isolates, being colocalised with *rmtB* (a 16S ribosomal RNA (rRNA) methylase conferring aminoglycoside resistance) in one transposon element [39].

Efflux in Gram-positive bacteria

The overexpression of multidrug efflux pumps also reduces the susceptibility to antibiotics in Gram-positives. The PmrA and PatAB efflux pumps (MFS) contribute to resistance to fluoroquinolones in *S. pneumoniae* [40, 41]. In *S. aureus*, low-level resistance to fluoroquinolones can be conferred by overexpression of the Nor family of MFS efflux pumps (NorA, NorB and NorC), whereas the AbcA and Tet38/TetK efflux pumps export β-lactams and tetracyclines, respectively [42]. An interesting link between these efflux pumps is represented by two regulators, MgrA (NorR) and NorG, with opposite effects: MgrA is a repressor of the Nor family efflux pumps and Tet38, but an activator of *abcA*, whereas NorG activates *norA*, *norB* and *norC*, but reduces the transcript level of *abcA* [43]. MepA is another multidrug transporter that is under the negative control of the MepR repressor and that confers resistance to tigecycline in *S. aureus*. Both genes are chromosomally located in the *mepRAB* operon (the function of the *mepB* gene is unknown) [44].

In *S. pneumoniae*, macrolide resistance can be caused either by the dual macrolide efflux protein A (Mef(A) and Mel) encoded by the transposon-associated *mefA* and *msrD* genes [45] or by the presence of *erm*(B) conferring methylation of the macrolide binding site (see the section on macrolides and lincosamides). The *erm*(B) gene is related to high-level resistance to macrolides, whereas the efflux-associated resistance shows lower MICs ($1–32\ mg{\cdot}L^{-1}$) and susceptibility to clindamycin (M phenotype). In *S. pneumoniae*, two genes, *spr1021* and *spr1887*, that encode for hypothetical ABC transporters were suggested to contribute to linezolid resistance [46].

The Msr(A), Msr(SA), Msr(SA)′ and Msr(B) efflux pumps found in *S. aureus* confer resistance to both macrolide and streptogramin B antibiotics [47], whereas the Qac efflux proteins export various monovalent and divalent antimicrobial cations, but not those antibiotics recommended for LRTI treatment. The *lmrS* gene of *S. aureus* encoding a putative MFS transporter has been shown to increase the MICs of different antimicrobials, with the highest being the MIC of linezolid when cloned into *E. coli*, and thus LmrS was suggested to be a multidrug efflux system in *S. aureus* [48].

Resistance to β-lactam antibiotics

β-Lactams include penicillins, β-lactamase inhibitors, monobactams, cephalosporins and carbapenems. Their primary target site is the cell wall. In Gram-negatives this is located in the periplasmic space, meaning that the β-lactam antibiotics must first diffuse through the outer membrane *via* the porins. In Gram-positives, β-lactams attack the cell wall directly [49]. A characteristic of β-lactam antibiotics is the β-lactam ring that mimics the D-alanyl-D-alanine structure, the natural substrate of membrane-associated

DD-transpeptidases (EC 3.4.16.4) involved in cell wall synthesis, cell division and cell growth [50]. As β-lactams covalently bind to those enzymes and thereby inhibit the enzymatic reaction, they are also called penicillin-binding proteins (PBPs). PBPs can be subdivided into high-molecular-weight and low-molecular-weight PBPs, but all share structural and phylogenetic similarities and are ubiquitous among Gram-negative and Gram-positive bacteria. However, their composition and orthologues differ between species.

Alterations of penicillin-binding proteins

Resistance to β-lactams in many Gram-positive bacteria, such as *S. pneumoniae*, is mainly caused by mutations in the PBPs that lead to reduced or lost binding of all β-lactams. *S. pneumoniae* can be equipped with up to six different PBPs. Four PBPs have been associated with penicillin resistance: PBP1a, PBP2a, PBP2x and PBP2b [51]. It is worth mentioning that the *pbp2X* and *pbp1a* genes, encoding for PBP2X and PBP1a, respectively, flank the *cps* locus that encodes for the modular organised genes responsible for the synthesis of the pneumococcal polysaccharide capsule. Thus, both the *pbp2X* and *pbp1a* genes are involved in the recombination processes of the *cps* locus, leading to epidemiological changes of the serotype and penicillin resistance prevalence [52]. Most *S. pneumoniae* isolates that are susceptible to benzylpenicillin are also susceptible to all other β-lactams. According to EUCAST, the clinical resistance breakpoint of benzylpenicillin is MIC $\geqslant$2 mg·L^{-1} (figure 1). The main mechanism of high-level resistance (MIC >4 mg·L^{-1}) to penicillins is related to amino acid substitutions in the active site motifs of PBPs (*i.e.* SXXK, HSXN and K[ST]G), whereas low-level resistance (MIC of benzylpenicillin 0.06–1 mg·L^{-1}) is related to various other substitutions within the PBPs, mainly in PBP1A, PBP2B and PBP2X [53, 54].

The vast majority of *S. aureus* isolates are penicillinase producers that are resistant to natural penicillins, aminopenicillins, carboxypenicillins and ureidopenicillins. The resistance to methicillin and related derivatives in *S. aureus* (MRSA) is due to the expression of PBP2a encoded by the *mecA* gene or its homologue *mecC*. The protein products of both function as a surrogate transpeptidase of the penicillin-sensitive PBP2 and are not present in methicillin-susceptible strains [55, 56]. PBP2a lacks transglycosylase activity, but it is resistant to the irreversible acylation by methicillin at the active serine residue (SXXK motif) and thus it complements the transpeptidase activity of PBP2 that becomes inactivated by methicillin [57]. Ceftaroline and ceftobiprole are novel MRSA-active β-lactam antibiotics that costimulate an allosteric opening of the active site, restoring the inactivation of PBP2a by a second β-lactam molecule [58]. The prevalence of MRSA in LRTIs, primarily in HAP, varies greatly between 1% and ∼30% depending on the country [23]. In a recent study investigating the worldwide (54 countries) prevalence of MRSA in hospitalised patients with CAP, on average a MRSA was identified within 24 h after hospital administration in 2.6% of patients, with a significantly increased prevalence in North America (4.8%) [59].

Reduced binding affinity of aminopenicillins and other β-lactams to altered PBPs (mainly the low-molecular-weight PBP3) has also been reported in β-lactamase-negative ampicillin-resistant (BLNAR) isolates of *H. influenzae* [60]. BLNAR isolates show reduced susceptibility to aminopenicillins, β-lactamase inhibitor combinations and some cephalosporins. Depending on the mutations in the *ftsI* gene, which encodes the transpeptidase domain of PBP3, the MICs of ampicillin and cephalosporins can vary between 0.5 and 16 mg·L^{-1} [61]. BLNAR isolates and isolates possessing both a β-lactamase and PBP3 phenotype, referred to as β-lactamase-positive amoxicillin–clavulanate resistant

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(BLPCAR), are rare (<10%), but are increasingly reported from different regions and seem to be strongly associated with respiratory tract infections [62–64]. The overall nonsusceptibility to amoxicillin has been reported as 16.4% for LRTI isolates collected in 2004/2005 in Europe [64].

β-Lactamases

The primary resistance mechanism to β-lactams in Gram-negative bacteria is production of β-lactamases. β-Lactamases are enzymes that are able to break the β-lactam ring through hydrolysis, thus rendering the antibiotic ineffective. β-Lactamases are a highly inhomogeneous group of enzymes that can be classified according to their protein sequence homology (Ambler classification) [65] into four classes: A (*e.g.* TEM and CTX-M variants), C (*e.g.* AmpC) and D (OXA variants) representing serine β-lactamases, and B representing metallo-β-lactamases (*e.g.* VIM or NDM variants). Based on their hydrolytic profile, β-lactamases can also subdivided into narrow-spectrum β-lactamases that hydrolyse penicillin (*e.g.* benzylpenicillin), and first- and second-generation cephalosporins (*e.g.* cefazolin and cefaclor, respectively); ESBLs that hydrolyse third- and fourth-generation cephalosporins (*e.g.* ceftazidime and cefepime, respectively); and carbapenemases hydrolysing last-resort β-lactams (*e.g.* meropenem and ertapenem). Additionally, β-lactamases may be susceptible or resistant to β-lactamase inhibitors (*e.g.* clavulanic acid and tazobactam). The hydrolytic spectrum is not associated with the Ambler classification; therefore, the Bush–Jacoby–Medeiros classification was introduced that also includes information on hydrolytic activity (table 2) [66]. β-Lactamases are often located on mobile elements such as transposons or plasmids and thus can be exchanged rapidly [67].

In β-lactamase-positive ampicillin-resistant (BLPAR) *H. influenzae* the narrow-spectrum resistance (susceptible to cephalosporins and carbapenems) is mediated predominantly by the plasmid-encoded TEM-1-like β-lactamase variants. The BLPAR *H. influenzae* isolates can be inhibited by β-lactamase inhibitors, such as clavulanic acid [61]. The prevalence of TEM-1-like β-lactamases varies depending on the geographical region, but was usually confirmed in >75% of BLPAR TEM-1 [62, 63, 68]. A second plasmid-borne β-lactamase variant with lower prevalence is ROB-1, which is related to an increased MIC of cefaclor [68]. Strains expressing both variants or ESBL phenotypes (resistance to third- and higher-generation cephalosporins) are rare [61].

More than 90% of *M. catarrhalis* isolates are resistant to penicillins, but sensitive to amoxicillin–clavulanic acid and cephalosporins [69]. The primary mechanism responsible for resistance to penicillins is production of the β-lactamases BRO-1 (90–95%) and BRO-2 (<10%) [70].

Gram-negative enterobacteria (GNEB), but also *A. baumannii* and *P. aeruginosa*, that produce a variety of plasmid-encoded β-lactamases have become increasingly nonsusceptible to cephalosporins and carbapenems. Furthermore, overexpression of chromosomally encoded β-lactamases is associated with resistance to β-lactams. For example, the intrinsic OXA-51-like variants in *A. baumannii* exhibit very low carbapenemase activity that does not result in phenotypic carbapenem resistance [17]. However, upstream insertion of IS (insertion sequence) elements can strongly increase the expression levels of chromosomally and plasmid-encoded variants, thereby increasing MICs against both cephalosporins and carbapenems [14, 18, 19]. These pathogens often carry several β-lactamase variants with different hydrolytic properties, rendering all β-lactams ineffective. Results from the international SENTRY Antimicrobial Surveillance Programme

Table 2. Classification of β-lactamases and their characteristics

Ambler class	Major clinically relevant β-lactamase groups	Bush–Jacoby–Medeiros class	Characteristics[#]
A	TEM, SHV[¶], CTX-M[+]	2b	Similar hydrolysis of benzylpenicillin and cephalosporins
		2be	Increased hydrolysis of oxyimino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam)
		2br	Resistance to clavulanic acid, sulbactam and tazobactam
		2ber	Increased hydrolysis of oxyimino-β-lactams combined with resistance to clavulanic acid, sulbactam and tazobactam
	KPC	2f	Increased hydrolysis of carbapenems, oxyimino-β-lactams, cephamycins
	CARB	2c	Increased hydrolysis of carbenicillin
B	VIM, NDM, IMP, IND	3a	Broad-spectrum hydrolysis including carbapenems, but not monobactams
C	CMY, MOX, MIR, FOX, ACT	1	Greater hydrolysis of cephalosporins than benzylpenicillin; hydrolyses cephamycins
		1e	Increased hydrolysis of ceftazidime and often other oxyimino-β-lactams
D	OXA	2d	Increased hydrolysis of cloxacillin or oxacillin
		2de	Hydrolyses cloxacillin or oxacillin and oxyimino-β-lactams
		2df	Hydrolyses cloxacillin or oxacillin and carbapenems

[#]: characteristics as defined by Bush and Jacoby [66]; [¶]: the SHV group does not contain 2ber phenotypes; [+]: variants of the CTX-M group are all 2be.

that analysed hospitalised patients with LRTIs (CAP and healthcare-associated pneumonia) between 2009 and 2012 in USA and Europe showed that ∼20–35% of *Klebsiella pneumoniae*, *E. coli* and *P. aeruginosa*, and 13–18% of *H. influence*, exhibited an ESBL phenotype [71]. Carbapenem resistance rates have been reported to be ∼10% in *K. pneumoniae* pneumonia isolates, and 25–40% in *A. baumannii* and *P. aeruginosa* [72]. It is worth noting that higher rates of ESBL- and carbapenemase-producing isolates vary greatly between geographical regions. ESBL-mediated β-lactam resistance in GNEB is primarily related to the CTX-M variants that are inhibited by β-lactamase inhibitors. However, many (30–50%) of the CTX-M-positive isolates produce additional β-lactamases (such as TEM or OXA) conferring resistance to tazobactam [73]. β-Lactamases found in *P. aeruginosa* are class C β-lactamases, variants of class A ESBLs (TEM, PER and VEB) as well as carbapenemases (mainly metallo-β-lactamases such as VIM, IND and NDM) [73–75]. In *A. baumannii*, the predominant β-lactamases leading to carbapenem resistance are OXA variants, followed by GES and KPC (both belonging to class A) [76].

 https://doi.org/10.1183/2312508X.10004416

Macrolides and lincosamides

Macrolide–lincosamide–streptogramin B (MLS_B) antibiotics have different structures, but all share a similar mode of action. Macrolides are natural products composed of a macrocyclic lactone ring to which sugars are attached. The most relevant macrolides in the treatment of LRTI are azithromycin, clarithromycin and erythromycin. Natural lincosamides (lincomycin) derive from pyranoses, but are currently produced and derivatised synthetically (*e.g.* clindamycin). Streptogramin B is a polypeptide antibiotic produced naturally by nonribosomal peptide synthesis.

MLS_B antibiotics bind reversibly to the 23S rRNA in the 50S subunit and block protein biosynthesis by preventing of peptidyltransferase activity, leading to dissociation and enrichment of peptidyl-transfer RNA (tRNA) and a toxic depletion of free tRNA [77]. Additionally, macrolides have been shown to inhibit quorum sensing and the production of some virulence factors, such as adhesins and alginate in *P. aeruginosa*, inhibiting or interfering with biofilm formation, but also to modulate inflammation and immunity in eukaryotes, thus indicating that these antimicrobials exhibit a complex biological activity with different sites of actions [78]. As macrolides are hydrophobic they can passively translocate across the outer and inner membranes. However, the polysaccharide moieties of lipid A in Gram-negatives represent an effective barrier against macrolides [79].

Macrolides, lincosamides and streptogramins are primarily active against Gram-positive bacteria. Methylation of 23S rRNA is one of the major resistance mechanisms against MLS_B antibiotics (MLS_B phenotype) in Gram-positive species, including *S. pneumoniae* and *S. aureus*. More than 40 different *erm* genes encoding the responsible methylases have been described, with *erm*(A) and *erm*(C) typically found in staphylococci and *erm*(B) in streptococci [47]. The *erm* genes are located on plasmids and can be transferred even between less-related species [80]. Furthermore, mutations in the domains V and II of the 23S rRNA and genes encoding riboproteins L4 and L22 are related to the increased MICs of macrolides, lincosamides and streptogramins in *S. pneumoniae* [81].

Other mechanisms, such as hydrolysis or modification of streptogramins or lincosamides, that lead to inactivation of antibiotics have been reported in staphylococci. Enzymes hydrolysing streptogramin B (virginiamycin factor B hydrolases) are coded by *vgb*(B) genes and lincomycin nucleotidyltransferase is coded by *lin*(A)′ [47].

Due to the macrolide efflux pump ArcAB, *H. influenzae* is intrinsically resistant (in 98% of the cases) to antibiotics of the MLS_B class. However, according to the MIC breakpoint, most *H. influenzae* isolates are classified as intermediately resistant to macrolides. A small proportion of *H. influenzae* isolates (<2% in both cases) shows hypersusceptibility (MIC azithromycin <0.25 $mg{\cdot}L^{-1}$) or hyperresistance (MIC azithromycin >4 $mg{\cdot}L^{-1}$) to macrolides [15]. A lack of the efflux was reported in some hypersusceptible isolates [82]; whereas hyperresistant isolates bear other macrolide resistance mechanisms, such as methylation or mutation in the 23S rRNA, or mutations in ribosomal proteins (L4 and L22) [61].

Resistance to fluoroquinolones

Fluoroquinolones interfere with DNA replication by binding to gyrase (an enzyme that controls the negative superhelical tension of the bacterial chromosome) and to

topoisomerase IV (which mediates decatenation of interlinked chromosomes after replication). Binding of fluoroquinolones to gyrase and topoisomerase IV results in double-stranded DNA breaks and finally cell death [83]. At neutral pH, fluoroquinolones can exist as completely uncharged molecules or zwitterions; thus, they can cross the membranes directly (80%), but also use the porin route (20%) [84]. As fluoroquinolones target the highly conserved replication mechanism they are active against a broad range of bacteria, including Gram-negative, Gram-positive and atypical bacteria, but are preferably used for the treatment of LRTIs caused by *S. pneumoniae*, *H. influenzae*, *P. aeruginosa* and *M. catarrhalis* [15, 85].

Resistance to fluoroquinolones can arise by stepwise mutations in discrete regions, known as quinolone resistance-determining regions (QRDRs), of the *parC*, *parE*, *gyrA* and *gyrB* genes, which encode the subunits of the conserved topoisomerase IV (C_2E_2) and gyrase (A_2B_2), respectively. This resistance mechanism can be found in nearly all bacterial pathogens, including *S. pneumoniae* [86], *S. aureus* [86], *H. influenzae* [88], *M. pneumoniae* [89], *Enterobacteriaceae* [83], *P. aeruginosa* [90], *L. pneumophila* [91] and *M. catarrhalis* [92].

The fist-step mutations occur either in the ParC subunit of topoisomerase IV (*S. pneumoniae* [93] and *S. aureus* [87]) or the GyrA subunit of the gyrase (*E. coli* and *H. influenza*), generally leading to a reduced susceptibility. The presence of a single-step mutation increases significantly the probability for acquisition of further mutations in the same gene or a second target gene, with the consequence that the MIC may reach a high level [83, 94]. MICs of isolates with first-step mutations can be lower than the clinical breakpoint concentration. Such isolates may not be detected by MIC testing [95]. Therefore, treatment of infections caused by first-step mutants selects for variants with fluoroquinolone resistance, resulting in treatment failure [96].

Additionally, plasmid-mediated quinolone resistance (PMQR), which is horizontally transferable and mediated by *qnr* genes, has been shown to significantly increase the MIC of fluoroquinolones in *Enterobacteriaceae* [97]. The *qnr* genes encode proteins that exhibit specific pentapeptide repeats, and protect the complex of DNA and DNA gyrase or topoisomerase IV from the inhibitory effect of fluoroquinolones [97].

Aminoglycosides

Aminoglycosides inhibit protein biosynthesis by binding to the bacterial ribosome (primary complex with the 30S subunit) and by disturbing the translation process leading to aberrant proteins. This process depends on the energy status of the cell (transmembrane electrical potential) and thus indirectly on oxygenic cell respiration [98]. Aminoglycosides are highly polar molecules, but pass through the outer membrane of Gram-negatives by self-promoted uptake in a magnesium-dependent manner. As a result of their large size, aminoglycosides are unlikely to diffuse through porin channels of Gram-negative bacteria or the cell wall of Gram-positives [99]. The transport across the cytoplasmic membrane depends upon the membrane potential and divalent cations, and thus chelating agents, hyperosmolarity, low pH and anaerobiosis limit the effectiveness of aminoglycosides [99]. They are primarily active against growing Gram-negative aerobic bacteria and also show antistaphylococcal activities. Common aminoglycosides used for LRTIs are tobramycin, amikacin and gentamicin, and these aminoglycosides are also available as inhaled antibiotics [100].

 https://doi.org/10.1183/2312508X.10004416

The main mechanisms of resistance to aminoglycosides are decreased uptake and/or accumulation of the drug in the cell and expression of enzymes inactivating the antibiotics by modifications, such as *N*-acetyltransferases (AACs), *O*-phosphotransferases (APHs) and *O*-nucleotidyltransferases (ANTs). These modifications lead to reduced affinity to the ribosome, but also reduce the permeability of aminoglycosides through the both membranes [99]. The genes coding for these enzymes are usually transferred on plasmids and transposons. *aac* genes are widespread among the *Enterobacteriaceae*, but have also been identified in *P. aeruginosa*, *A. baumannii* and *S. aureus*. The specificity to the respective aminoglycoside may vary depending on the *aac* gene present [101]. APH modifies aminoglycosides in an ATP-dependent manner and is mainly related to *Enterobacteriaceae*. In *S. aureus*, a recombinant enzyme (AAC(6′)–APH(2″)) was identified conferring resistance to clinically relevant aminoglycosides [102]. Various genes coding for ANTs are also widespread in Gram-negatives and some in staphylococci [101].

In *Enterobacteriaceae* and in nonfermenting Gram-negative species, plasmid-encoded 16S rRNA methylases (*armA*, *rmtA*, *rmtB* and *rmtC*) that are associated with genes for ESBLs have also been shown to confer resistance to aminoglycosides [103].

The exposure to aminoglycosides additionally leads to adaptive resistances within a few hours in *P. aeruginosa* and other Gram-negative bacteria. These phenotypic resistances are most likely caused by changes in the protein composition of the membrane and the respiratory status [99].

Resistance to tetracyclines

The natural tetracycline antibiotics, such as tetracycline, oxytetracycline or demeclocycline, are produced by various *Streptomyces* spp. by nonribosomal peptide synthesis and represent a subclass of lipophilic polyketides [28]. Common semisynthetic products with increased lipid solubility are minocycline or doxycycline.

Tetracyclines prevent the binding of aminoacyl-tRNA to the bacterial ribosome and therefore inhibit protein biosynthesis. Thus, their site of action is in the cytoplasm. In Gram-negatives they cross the outer membrane through the porins as positively charged cations by complexing metal ions. In the periplasm, the metal ions dissociate and the free lipophilic tetracyclines can pass through the cytoplasmic membrane [28].

In addition to the efflux pumps, tetracycline resistance can be obtained by ribosomal protection proteins that are homologous to the elongation factors EF-Tu and EF-G. This mechanism is primarily found in Gram-positive bacteria. In *S. pneumoniae* and *S. aureus* these ribosomal protection proteins are coded by the transposon-located *tet*(M) gene and sporadically the *tet*(O) gene; however, Tet(M) has also been found in tetracycline-resistant *H. influenzae* [28].

Tigecycline is structurally related to the tetracyclines and exhibits a similar mode of action, but has a higher affinity to the ribosome. It can overcome most of the known tetracycline resistance mechanisms due to the bulky side group [104].

In terms of MICs, these resistance determinants confer a higher level of resistance to doxycycline and minocycline than efflux-related determinants [28]. High rates of tetracycline resistance among *S. pneumoniae* isolates from patients with LRTIs have been

reported in many regions; thus, tetracyclines have become less important in empiric initial therapy [15]. The spread of tetracycline resistance seems to be related to the distribution of a specific conjugative transposon [105, 106].

Chloramphenicol

Chloramphenicol is an inhibitor of protein biosynthesis. The mode of action is complex. It is thought to interfere with the mRNA bound to the 30S ribosome subunit in a sequence-dependent manner, but also to reversibly bind to the peptidyltransferase centre (PTC) and inhibit the final condensation of amino acids at the 50S ribosome subunit [33, 107]. Chloramphenicol is active against a broad range of pathogens, including Gram-positive and Gram-negative bacteria, and *Chlamydia* and *Mycoplasma* spp. [33].

Resistance to chloramphenicol has a polygenic character. In addition to effective efflux, it is also associated with the presence of the *cat* genes that code for chloramphenicol acetyltransferases. This enzyme family inactivates chloramphenicol by acetylation [33] and contains many enzyme variants that are widespread in different genera. The *cat* genes may be found on chromosomes, but are usually located on resistance plasmids carrying at least one other resistance determinant. For example, in *S. pneumoniae* the *catQ* gene is associated with the *mef*(I) gene that encodes an alternative macrolide efflux pump; both are located on an integrative and conjugative transposon-like element (ICE) that was only identified in streptococci and is known as the IQ module [108]. The ICEs may also contain the *tet*(M) gene, and thus chloramphenicol resistance in *S. pneumoniae* is often associated with an increased MIC to macrolides and/or tetracyclines [106].

Cotrimoxazole

Cotrimoxazole is an antibiotic formulation that combines trimethoprim and sulfamethoxazole (a sulfonamide antibiotic). Both antibiotics inhibit the biosynthesis of tetrahydrofolate but have different targets. Tetrahydrofolate is a general 1-carbon carrier and plays an essential role in many processes in the cell, such as a ribonucleotide and in amino acid synthesis. Sulfamethoxazole is a substrate analogue of dihydropteroate synthetase (DHPS) and inhibits the conversion of *p*-aminobenzoic acid and dihydropteroate diphosphate to dihydrofolate, whereas trimethoprim inhibits dihydrofolate reductase (DHFR), the subsequent step of tetrahydrofolate synthesis [109]. Both antimicrobials act synergistically and thus are usually administered in combination [110]. Cotrimoxazole covers a wide spectrum of bacteria (*e.g. Enterobacteriaceae*, *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, *L. pneumophila*, *Chlamydia* spp., *P. aeruginosa*, *Pasteurella multocida*, *S. pneumoniae*, *S. aureus*, *Nocardia* spp. and *Listeria* spp.), protozoa (*e.g. Cyclospora* spp. and *Toxoplasma gondii*) and even the fungus *Pneumocystis jirovecii.*

Resistance to cotrimoxazole in *P. aeruginosa* [38, 111] and *K. pneumoniae* [112] is associated with reduced permeability and efflux mechanisms (table 1). As a consequence of the high MIC values of cotrimoxazole, no breakpoint has been proposed for *P. aeruginosa* by EUCAST.

DHFRs with lower binding affinity to trimethoprim were found in *M. catarrhalis* [112], *S. aureus* [113] and *S. pneumoniae* [114]. These altered DHFRs result from a single or a few mutations in the *dhfr* genes. Some DHFRs are naturally insensitive to trimethoprim (*e.g.* in *M. catarrhalis)*. In cotrimoxazole-resistant *H. influenzae*, both overproduction of DHFR due to mutations in the promoter and altered DHFR were found [115]. Additionally, mutations in the *dhps* genes may lead to DHPS resistance to sulfonamides and have been

 https://doi.org/10.1183/2312508X.10004416

reported in a number of different species, including *E. coli*, *S. pneumoniae* and *S. aureus* [112].

The prevalence of cotrimoxazole resistance in LRTI pathogens varies greatly between studies, but in general can be expected mainly in *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* [112].

Glycopeptides

Vancomycin and teicoplanin are natural glycopeptides, whereas telavancin, dalbavancin and oritavancin (lipoglycopeptides) are semisynthetic derivatives [116]. Glycopeptides bind to the L-Lys–D-Ala–D-Ala precursor of the peptidoglycan, preventing cross-linkage of the peptidoglycan layers in Gram-positive bacteria [117].

Resistance to glycopeptide antibiotics is associated with *van* gene clusters that are transferred on transposons and code for various enzymes whose expression results in remodelling of the cell wall. Resistance to vancomycin is predominantly found in *Enterococcus faecium* and is still very rare in *S. aureus*. Most likely, the occurrence of high-level vancomycin-resistant *S. aureus* resulted from the transfer of the *vanA* gene cluster from *E. faecium via* conjugation of a plasmid-borne Tn*1546* element [118]. VanA confers resistance to vancomycin and teicoplanin [116]. It carries one inducible operon with three genes encoding the enzymes VanH, VanA and VanX that result in an altered L-Lys–D-Ala–D-Lac precursor. This operon is under the control of the two-component system VanRS located upstream. Thereby, VanS is the His kinase that becomes activated (*via* dimerisation and autophosphorylation) by vancomycin, but not by teicoplanin, and activates the response regulator VanR. An activated (phosphorylated) VanR dimer binds at the promoter of the *van* operon and activates the transcription. Two accessory genes are located downstream of the *van* operon, *vanY* and *vanZ*, which contribute to high-level resistance against vancomycin and teicoplanin. Similar to VanX, VanY is a carboxypeptidase that hydrolyses the last D-Ala of the original precursor. The function of VanZ is unknown, but it confers low-level teicoplanin resistance in the absence of the *van* operon [119].

Colistin

Polymyxins, such as colistin (polymyxin E) and polymyxin B, are cyclic nonribosomal lipopolypeptide antibiotics with activity against selected Gram-negative bacteria, including *E. coli*, *K. pneumoniae*, *H. influenzae*, *P. aeruginosa* and *A. baumannii* [120]. Some Gram-negative bacteria, such as *Proteus*, *Serratia* and *Burkholderia* spp., as well as Gram-positive species are inherently resistant to polymyxins. Polymyxins are amphiphilic molecules with a detergent-like mode of action. They interact with hydrophobic (lipids) but also anionic polysaccharides of lipid A, which is the main compound of the outer membrane of Gram-negatives. This results in lethal destabilisation and disruption of the outer membrane [121].

Colistin resistance is rare within the susceptible species, but modification of lipid A that decreases its negative charge represents the main resistance mechanism against polymyxins. The most common modification is the incorporation of 4-amino-4-deoxy-L-arabinose (Ara4N) into lipid A [122], followed by addition of phosphoethanolamine (PEtN). In *P. aeruginosa* and other Gram-negatives this could be related to the operons *arnBCADTEF–pmrE* and *pmrCAB*, respectively [123]. The *arn* operon encodes proteins and enzymes for Ara4N synthesis and the *pmr* operon encodes proteins and enzymes for PEtN synthesis.

The regulation of both is colistin inducible, and occurs directly (PmrA/PmrB and PmrE) and indirectly (PhoQ/PhoP) *via* different regulators in an adaptive manner; thus, mutations in the regulatory proteins have been shown to contribute to colistin resistance [122].

While these resistances are chromosomally encoded, the *mcr-1* and the recently identified *mcr-2* genes were found on plasmids and encode PEtN transferases [124, 125]. Both were isolated primarily from animal specimens, but *mcr-1* had already been determined in humans in some regions. Plasmids carrying *mcr* genes have been shown to be particularly highly transferable across Gram-negatives [124, 125]. Thus, it is to be feared that resistance to colistin will increase, although the *mcr* genes are not yet widely disseminated.

Linezolid

Linezolid belongs to the oxazolidinone class of antimicrobials that are primarily active against Gram-positive bacteria. Linezolid binds to the ribosomal 50S subunit preventing the formation of the initial translational complex with the 30S subunit, mRNA and formylmethionyl-tRNA [126]. In general, the ribosomes of Gram-negative bacteria are also sensitive to linezolid, but due to the highly effective efflux of the drug, Gram-negatives exhibit a resistant phenotype. In *E. coli* this could be related to the ArcAB–TolC efflux pumps [127].

Linezolid resistance in *S. aureus*, *E. faecium* and *Enterococcus faecalis* is caused mainly by mutations of the 23S rRNA and the ribosomal protein L3. Modifications of the 23S rRNA by methyltransferases (*e.g.* RlmN *S. aureus* [128], RlmL in *E. coli* [129] or spr0333 in *S. pneumoniae* [46]) and pseudouridine synthase (*e.g.* RluE and RLuB in *E. coli* [129]) confer resistance to linezolid, but also to other antibiotics which bind to the ribosomal PTC ("PTC antibiotics") such as clindamycin and tiamulin [129] in different bacteria species. Most of these enzymes are chromosomally located, whereas Cfr represent a transferable methyltransferase that confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A antibiotics ($PhLOPS_A$ phenotype), and was found in Gram-positives (*S. aureus* and *E. faecalis*) and Gram-negatives (*Proteus vulgaris*) [130]. The binding site of linezolid at the 23S rRNA subunit is different from that of the MLS_B antibiotics and thus it is not affected by the activity of the *erm*-encoded methylases [130].

Conclusions

Although general resistance principles (*i.e.* decreased influx, increased efflux, modified target site and antibiotic-modifying enzymes) are limited in number, there is a huge variety of different mechanisms for each principle. Antibiotic resistance is a feature of bacterial evolution, and therefore highly dynamic and unpredictable. While antibiotic-modifying enzymes and target modification have been considered the main principles of resistance, the role of increased efflux and decreased influx that usually confer lower level resistance may have been underestimated. In particular, the combination of several resistance mechanisms in a single isolate, which seems to occur increasingly frequently, is a challenge, *e.g.* in molecular diagnostics or the development of novel antibiotics. Antibiotic tolerance due to biofilm formation additionally complicates both diagnostics and treatment. Therefore, these mechanisms of resistance and tolerance are currently being specifically addressed in many major research initiatives.

 https://doi.org/10.1183/2312508X.10004416

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Disclosures: M.W. Pletz has received grants from the German Research Foundation, the German Ministry for Science and Education, Biotest, InfectoPharm and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Biotest, Clinigen, InfectoPharm, MSD, Pfizer and Thermo Fisher, and has a patent "Measuring antibiotic blood levels with Raman spectroscopy" pending.

Chapter 3

Antibiotics in critical care: dosing, therapeutic drug monitoring and continuous infusions

Maya Hites[1] and Fabio Silvio Taccone[2]

Critically ill patients are particularly vulnerable to develop infections and these infections may be caused by pathogens with reduced susceptibility to currently available antibiotics. Rapid, adequate and appropriate individualised antibiotic therapy can help improve outcomes in these patients, and in this chapter we discuss how to optimise this treatment. In order to deliver this kind of therapy, rapid and accurate diagnosis of infection and identification of infecting pathogens and their antibiotic susceptibilities is necessary. This may be facilitated by using new technologies such as MALDI-TOF (matrix-assisted laser desorption ionisation time-of-flight) mass spectrometry and PCR techniques. As the pharmacokinetics of drugs is unpredictable in infected, critically ill patients, routine therapeutic drug monitoring of antibiotics should be considered whenever possible to optimise therapeutic efficacy and reduce risk of toxicity. In order to improve therapeutic efficacy, antibiotics may be given with higher loading doses, in continuous perfusion or by inhalation.

Cite as: Hites M, Taccone FS. Antibiotics in critical care: dosing, therapeutic drug monitoring and continuous infusions. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 44–56 [https://doi.org/10.1183/2312508X.10004516].

The aim of this chapter is to provide insights on how to optimise antibiotic therapy in the critically ill patient. To begin with, we discuss why the critically ill patient is so different from other patients. We then discuss the importance of: 1) rapid diagnosis of infection with rapid identification of causative organisms and their antibiotic susceptibilities, and 2) appropriate and adequate antibiotic therapy. Finally, we provide suggestions for optimising antibiotic dosage regimens in this special patient population, including therapeutic drug monitoring (TDM), prolonged or continuous infusions and aerosolised administration of certain antibiotics, and consider the risk of toxicity.

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The critically ill patient

The critically ill patient is an extremely vulnerable and complex patient, who often suffers from infections. Between 11% and 27% of patients are admitted to the ICU for a severe infection [1–5], and all patients admitted to the ICU (even those admitted for noninfectious causes) are at great risk of developing an infection during their stay [6, 7]. Critically ill patients are particularly vulnerable to develop infections because they present a certain degree of immune dysfunction [8–10], they undergo many invasive procedures and they often carry multiple catheters (urinary, arterial and venous). Furthermore, in infections developed in the ICU, bacterial inoculum tends to be greater and infecting pathogens tend to be less susceptible to antibiotics than in infections developed outside of the ICU [11–13].

Early, appropriate and adequate antibiotic therapy is necessary to treat these infections in order to improve outcomes (figure 1). "Early" refers to the need to give appropriate antibiotics within the first hour of documented hypotension in the case of sepsis, because a progressive increase in mortality (*e.g.* ~7%) has been observed with every additional hour of delay [14]. However, a recent meta-analysis has challenged these observations, as no significant mortality benefit was observed when antibiotics were administered within 1 h of shock recognition [15]. Differences in observations may be due to the fact that the authors of the meta-analysis did not evaluate whether patients had received effective or "appropriate" antibiotic therapy. "Appropriate" means that the antibiotic(s) administered is (are) active *in vitro* against the pathogen(s) responsible for the infection. Indeed, inappropriate choice in empirical antibiotic therapy, for a wide variety of severe infections, would result in increased patient mortality [16–19]. "Adequate" therapy means also that the dosage regimen administered will allow for rapid, sufficient antibiotic concentrations at the site of the infection, to treat the infection in an optimal fashion. Once again, studies have shown poorer outcomes when infections were treated with standard dosage regimens of antimicrobials and caused by bacteria with higher than usual MICs of the antibiotic administered [20–22].

Diagnosing and treating infections in the critically ill patient can nevertheless be very challenging for the clinician. Typical signs of infection are not sensitive, as they may be lacking in the critically ill patient (*e.g.* fever), and they are not specific, as they may be observed in other health conditions also observed in the ICU (*e.g.* pancreatitis, drug-related

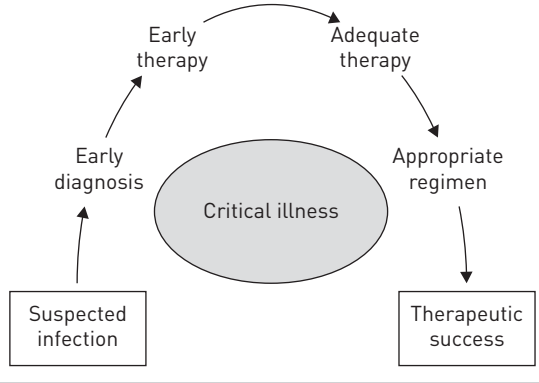

Figure 1. Schematic representation of the characteristics of antibiotic therapy during critical illness that might increase the likelihood of therapeutic success.

or central fever). Moreover, results from microbiology tests may take several days and may remain negative if the patient has received recent previous antibiotic therapy.

Furthermore, the worldwide increase in antimicrobial resistance makes it difficult to administer appropriate and adequate empiric antibiotic therapy. There has been a general and significant increase in the number of pathogens resistant to antibiotics worldwide ever since the utilisation of the first antibiotics (sulfamides) in humans in the early 1900s. Many different classes of antibiotics (with different modes of action) were developed and commercialised from the 1940s until the late 1990s. However, the previously flowing pipeline of new antibiotics has currently floundered to a trickle [23], leaving clinicians with few therapeutic choices for certain infections. To illustrate this phenomenon, we can take a closer look at antibiotic resistance in Europe. For *Klebsiella pneumoniae*, resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides, but also combined resistance to all three antibiotic groups, significantly increased from 2006 until 2014. For *Escherichia coli*, population-weighted (European Union and Economic Area) mean percentage of resistance to third-generation cephalosporins increased from 9.6% in 2011 to 12% in 2014. For *Pseudomonas aeruginosa*, the number of countries with >25–50% of strains resistant to carbapenems more than doubled from 2006 to 2014. For *Staphylococcus aureus*, although the percentage of MRSA strains has diminished since 2004, seven out of 29 European countries still reported population-weighted mean percentages >25% in 2014 [24]. Finally, the prevalence of carbapenem-resistant *Enterobacteriaceae*, responsible for almost untreatable infections, has increased significantly in Europe (particularly in Greece and Italy), the USA, South America and Asia since the isolation of the first carbapenem-resistant *Enterobacteriaceae* strain in the USA in 1996 [25].

To further complicate matters, the critically ill patient presents many physiological changes responsible for changes in volume of distribution and drug clearance, and thus of their pharmacokinetics (figure 2). The volume of distribution of a drug is the theoretical volume in which the drug distributes. The extent of the distribution of the drug will depend on its

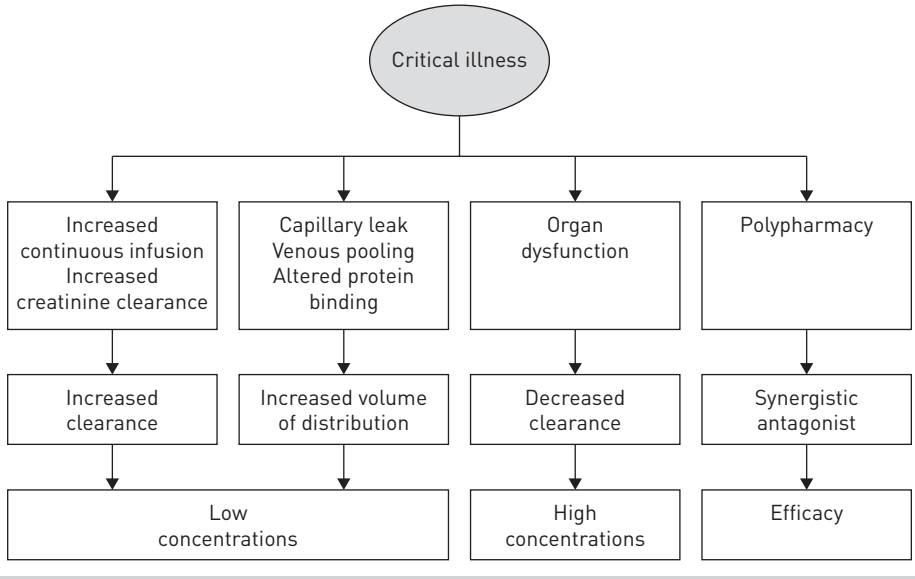

Figure 2. Alterations in antibiotic pharmacokinetics during critical illness.

https://doi.org/10.1183/2312508X.10004516

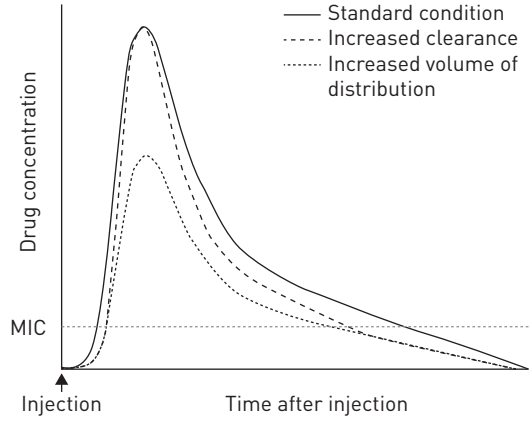

Figure 3. Effects of changes in antibiotic pharmacokinetics during critical illness on drug concentrations. Compared with the standard condition, an increase in drug clearance will result in a lower duration of drug concentrations above the MIC of the pathogen. In the case of an increased volume of distribution, the maximum concentration after drug injection will be reduced.

structure (*e.g.* lipo- or hydrophilicity), protein binding and molecular weight. Increased cardiac output, interstitial fluid shifts associated with increased capillary leakage, fluid resuscitation, hypoalbuminaemia and drains are responsible for an increased volume of distribution of hydrophilic antibiotics, and thus decreased antibiotic plasma levels (figure 3). The volume of distribution of lipophilic drugs is hardly modified by these physiological changes. Also, as hydrophilic drugs are essentially eliminated by the kidneys, changes in renal function will affect drug clearance; as such, hyperdynamic status and increased renal blood flow could result in lower than expected plasma concentrations than in patients who are not critically ill. However, organ dysfunction (*e.g.* renal or hepatic) may also develop and contribute to drug accumulation [26]. Patients may also benefit from different extracorporeal devices (*e.g.* continuous renal replacement therapy or extracorporeal membrane oxygenation), thus further interfering with the pharmacokinetics of antibiotics [27]. Lipophilic drugs are essentially eliminated from the body by hepatic metabolism; drug clearance may be slower when patients present hepatic insufficiency [28]. These potential pharmacokinetics variations in the critically ill patient are highly unpredictable.

How to improve empiric antibiotic treatment

There are several ways to try to improve empiric antibiotic therapy: 1) the diagnosis of sepsis and its causative pathogens must be done more rapidly, and with more precision, and 2) the spectrum of empiric antibiotic therapy can be broadened by administering combination therapy.

Diagnosis

The diagnosis of infection and then the administration of the appropriate antibiotic to treat the infection in the critically ill patient rely heavily on results from the microbiology laboratory. It can take several days to obtain positive results as most tests currently depend on culture-based techniques. However, new techniques are being developed to shorten the laboratory turnaround time for providing results. MALDI-TOF (matrix-assisted laser

desorption ionisation time-of-flight) mass spectrometry has been shown to rapidly detect ESBL-producing *Enterobacteriaceae* from positive blood cultures with a sensitivity of 99% after 90–150 min [29], and to detect carbapenemase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa* in blood cultures within 4.5 h with high sensitivity and specificity [30]. PCR is another available molecular diagnostics assay that identifies pathogen DNA and resistance markers within hours [31–33]. However, these techniques do not differentiate infecting pathogens from colonisation, and they may underdiagnose infections when they are not accompanied by bloodstream infection. Furthermore, although the use of such techniques has been shown to decrease hospital and ICU length of stay, and total hospital costs, only a small selection of ESBLs and carbapenemases can be identified by these diagnostic tests, which are also costly [34].

Combination therapy

Combination antibiotic therapy could help improve the efficacy of empiric therapy by offering a broader antibiotic coverage compared with monotherapy [35], by providing possible *in vitro* antibacterial synergy (thus resulting in increased bacterial killing) [36] and by preventing emergence of resistance [37]. However, combination therapy may also have some potential disadvantages: increased risk of toxicity, increased costs, possible *in vitro* antibacterial antagonism (thus resulting in decreased bacterial killing) and increased risk of superinfections due to extremely resistant pathogens.

In retrospective or observational studies, mortality rates were significantly lower in patients treated with combination therapies compared with monotherapy for septic shock, infections due to MDR Gram-negative pathogens and CAP [38–41]. A meta-analytic/regression study showed that combination therapy for sepsis or septic shock was consistently associated with improved outcome in those patients with an expected mortality >25% [42]. However, RCTs have failed to confirm these findings. Indeed, meropenem and ciprofloxacin given in combination did not improve patient outcome when compared with treatment with meropenem alone in an RCT including 740 patients with suspected VAP [43], and meropenem and moxifloxacin given in combination did not improve patient outcome either when compared with meropenem alone in another RCT including 600 septic patients [44]. In both studies, patient populations were very heterogeneous and the majority of pathogens were susceptible to meropenem, but 20–30% of strains were resistant to fluoroquinolones, making it difficult to demonstrate a benefit with combination therapy. Finally, in an RCT for patients hospitalised (but not in the ICU) with CAP in the Netherlands, patients received either β-lactams alone (n=656), β-lactams in combination with macrolides (n=739) or fluoroquinolones alone (n=888). No differences in the 90-day mortality were observed between patient groups, although clinical stability at 7 days of treatment was better (41% *versus* 34%; p=0.07) and 30-day readmission was lower (8% *versus* 3%; p= 0.01) in patients treated with combination therapy compared with the monotherapy arm [45]. Combination therapy should be considered in patients with septic shock and severe CAP or in patients with suspicion of infections due to MDR pathogens. The most effective combination therapy remains controversial.

Optimisation of antibiotic dosing in the critically ill

When considering optimising antibiotic therapy, it is important to introduce some concepts on the pharmacokinetics/pharmacodynamics of drugs. Pharmacokinetics is the study of the relationship between the dose of drug administered and the concentration of

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the drug observed over time in the body fluids (*i.e.* essentially the blood compartment) and tissues. Drug concentrations that are commonly used to describe antibiotic pharmacokinetics are the trough concentration (C_{min}, *i.e.* the minimum concentration before the next dose), the peak concentration (C_{max}, *i.e.* the maximum concentration after a bolus administration) and the AUC. Pharmacodynamics is the study of the *in vivo* effect that the antibiotic has at a given concentration to kill or to inhibit the growth of bacteria. The MIC is the minimum antibiotic concentration that results in the inhibition of bacterial growth under standard conditions and is commonly used to quantify the pathogen's response to the antibiotic. Thus, pharmacokinetics/pharmacodynamics is the relationship between dose and effect. The efficacy of each antibiotic will be best described by a specific pharmacokinetics/pharmacodynamics index. The main pharmacokinetics/pharmacodynamics indices are: 1) for time-dependent antibiotics: the time that the serum concentration of the unbound fraction of the antibiotic remains above the MIC ($fT_{>MIC}$), 2) for concentration-dependent antibiotics: the ratio of the peak concentration to the MIC (C_{max}/MIC) during one dosing interval, and 3) for concentration-dependent antibiotics with time dependency: the ratio of the AUC of the unbound fraction of the antibiotic from 0 to 24 h to the MIC ($AUC_{0–24\,h}$/MIC). Specific pharmacodynamics targets have been identified for most antibiotics to ensure optimal efficacy (table 1) [46].

In order to improve pharmacodynamics target attainment, antibiotics can be administered with increased doses, increased frequency, prolonged infusion or continuous infusion.

Table 1. Pharmacokinetics/pharmacodynamics indices that describe the efficacy of different antibiotics and their specific pharmacodynamics targets

Index	Antibiotic	Pharmacodynamics target	Ways to improve pharmacodynamics target attainment
Time-dependent antibiotics: $fT_{>MIC}$	β-Lactams	$fT_{>4–5\times MIC}$ for 50–100% of the time [47]	Administer antibiotics with increased frequency, or in prolonged or continuous infusions
Concentration-dependent antibiotics: C_{max}/MIC	Aminoglycosides	C_{max}/MIC >8–10 [48]	Increase bolus dosage regimen
Concentration-dependent antibiotics with time dependency: $AUC_{0–24\,h}$/MIC	Vancomycin	$AUC_{0–24\,h}$/MIC >400 [49]	Increase loading dose, and administer with greater frequency, or in prolonged or continuous infusions
	Colistin	Unknown [50]	
	Fluoroquinolones	C_{max}/MIC >10 or $AUC_{0–24\,h}$/MIC >125 [51]	
	Daptomycin	$AUC_{0–24\,h}$/MIC >600 [52]	
	Linezolid	$AUC_{0–24\,h}$/MIC >80–120 [53]	
	Tigecycline	Skin infections: $AUC_{0–24\,h}$/MIC >17.9; abdominal infections: $AUC_{0–24\,h}$/MIC >6.96 [54]	

$fT_{>MIC}$: time that the serum concentration of the unbound fraction of the antibiotic remains above the MIC of the pathogen; C_{max}/MIC: ratio of the peak concentration to the MIC during one dosing interval; $AUC_{0–24\,h}$/MIC: ratio of the AUC of the unbound fraction of the antibiotic from 0 to 24 h to the MIC.

Treatment can also be guided by TDM, as illustrated by a case report of a patient with a severe infection due to a very resistant strain of *P. aeruginosa*. The patient needed 3 g meropenem every 6 h in 3-h extended infusions to be cured of his infection and survive [55]. Several studies have shown that pharmacokinetics/pharmacodynamics target attainment is improved when administering glycopeptides or β-lactams as prolonged or continuous infusion, compared with standard bolus dosing [56, 57]. Continuous infusion of β-lactams can rapidly achieve adequate drug concentrations for all susceptible Gram-negative strains, even in critically ill patients [58, 59].

Increased dosage regimens

Several studies have shown that when standard dosage regimens are given, serum concentrations of different antibiotics, such as β-lactams [60], amikacin [61] and vancomycin [48], are largely insufficient to treat patients in septic shock. Population pharmacokinetics analysis and Monte Carlo simulations of clinical data obtained from patients in septic shock have suggested the need for greater loading doses in septic patients. Clinical validation studies have then shown that pharmacokinetics/pharmacodynamics targets are more rapidly attained in septic patients who receive a loading dose of 25 $mg \cdot kg^{-1}$ for amikacin, instead of the previously recommended dose of 15 $mg \cdot kg^{-1}$ [61], and a loading dose of 35 $mg \cdot kg^{-1}$ for vancomycin [62, 63]. However, no study has yet shown that these new dosage regimens result in better clinical outcomes.

Therapeutic drug monitoring

TDM is based on direct measurement of serum antibiotic concentrations with timely feedback to clinicians who then interpret the results in terms of therapeutic ranges. Traditionally, TDM is used to minimise toxic effects, but in critically ill patients it can be used to optimise dosing in the presence of severely altered and unpredictable pharmacokinetics. For ideal TDM, the antibiotic MIC values for the infecting pathogen should be available.

Routine TDM in the critically ill patient is most frequently performed for aminoglycosides [64–67] and glycopeptides [68, 69]. It is less frequently performed for β-lactams [70], ciprofloxacin [71], linezolid [72] and colistin [73], despite the fact that a study on TDM of β-lactams including 236 critically ill patients showed that three-quarters of patients needed a dose adjustment, with 50% of the patients needing a dose increase after the first TDM to optimally treat their infection [74]. In an observational study on 638 patients with nosocomial pneumonia (205 patients benefitted from TDM and isolate MIC determination), receiving β-lactams, aminoglycosides or fluoroquinolones, the probability of good clinical outcome and pathogen eradication was significantly higher in patients who benefitted from TDM and isolate MIC determination than those who did not [75]. Only one RCT comparing the use of TDM *versus* no TDM has been performed; outcome was better in patients who benefitted from TDM of vancomycin [68]. Furthermore, a systematic review and meta-analysis of TDM of vancomycin (one RCT [68] and five cohort studies) was performed, concerning a total of 521 patients (249 managed with TDM and 272 managed without TDM). The authors found that TDM of vancomycin significantly increased the rate of clinical efficacy and decreased the rate of nephrotoxicity [76].

Although TDM may help to better attain pharmacokinetics/pharmacodynamics targets, suboptimal exposure may persist. Instead of adjusting doses based only on TDM and clinical judgement, more precise dose predictions can be obtained with the application of population pharmacokinetics models. These models describe the relationship between the

 https://doi.org/10.1183/2312508X.10004516

dose, serum concentrations and clinical covariates in a specific patient population. Prior pharmacokinetics information from the model can be used to estimate pharmacokinetics parameters of a specific patient using the clinical covariates and then make a precise dose prediction for the patient [77]. Dose prediction can be further improved using a Bayesian estimation approach. In other words, the pharmacokinetics parameter estimation can be refined by feedback from TDM so that the model will then better describe the population data and the patient. However, the precision of the dose predictions will depend on the quality of the population pharmacokinetics model. If the model does not accurately describe the specific patient population, dose predictions will not be accurate. Even when the best population model is chosen, prediction performance can be variable, justifying the need to perform clinical validation of the population models used in daily clinical practice [78, 79].

Finally, TDM may also be used very specifically to guide treatment of infections due to very resistant pathogens, as illustrated in a case series of 15 critically ill patients treated with high-dose aminoglycoside therapy combined with continuous renal replacement therapy. Despite very severely ill patients and infections due to very resistant pathogens, six patients were discharged alive from the ICU [80].

There are still limitations for the widespread use of TDM of β-lactams in routine clinical management of such patients. First, all of the chromatographic assays used have been developed "in-house" and no commercial kits are available. Moreover, wide variability between the reported meropenem and piperacillin concentrations from the same sample in different laboratories could be found, which suggests the need for a better external quality assessment of these bespoke chromatographic methods [81].

Prolonged and continuous infusions

A total of 182 patients receiving piperacillin–tazobactam and meropenem were analysed in the database of the DALI (Defining antibiotic levels in ICU patients) study. In one subgroup of patients with respiratory infection and the other subgroup with high severity of disease, continuous infusion of β-lactams resulted in significantly better 30-day survival when compared with standard dosage regimens (86% *versus* 57%; p = 0.012 and 73% *versus* 35%; p=0.0035, respectively) [82]. Also, in a randomised open-label controlled trial of continuous infusion *versus* intermittent infusion of meropenem in critically ill patients, a similar clinical outcome, but with superior microbiological efficacy, was achieved in the continuous infusion group, despite higher daily doses of meropenem in the intermittent group (6 *versus* 4 g·day^{-1}) [83]. A recent systematic review of randomised trials comparing continuous infusion *versus* intermittent infusion of β-lactams for the treatment of severe infections showed that continuous infusion was associated with decreased hospital mortality [84]. However, drug concentrations were not measured in all patients, which would limit the association between optimised drug levels and outcome in this setting. Moreover, continuous infusion did not result in better outcomes in an RCT of continuous infusion of vancomycin compared with standard therapy in patients with severe infections due to MRSA [85].

Mortality has been considered the best end-point in clinical trials in the ICU, but in reality it is not always such a clear binary end-point because mortality is often predicted by other factors already present at the time of ICU admission. Most RCTs using mortality as the primary end-point have resulted in negative results; however, despite the negative results, in each arm of the RCTs, some patients have benefitted and others have been harmed by the

intervention. A new way of approaching RCTs is to take several or multiple factors into account when evaluating an intervention; they should be individualised on the basis of specific pathophysiological considerations. Ideally, in the case of studies comparing intermittent infusions *versus* continuous infusion, patients with renal failure should be excluded and only patients with infections due to pathogens with higher MICs should be included. Furthermore, TDM and measurement of MICs of the infecting pathogen could be included in the study design to better link outcome to pharmacokinetics/pharmacodynamics targets.

Inhaled antibiotics

Inhaled antibiotics are another potential way of improving antibiotic delivery to critically ill patients with MDR Gram-negative pathogens or VAP in addition to systemic antibiotic therapy. Systemically administered antibiotics used to treat these infections often penetrate poorly into the lung parenchyma, and their therapeutic window between efficacy and toxicity may be narrow, whereas nebulised antibiotics may achieve airway antibiotic concentrations 100–300 times higher than the MICs of most bacteria, even MDR pathogens [86]. For example, aerosol administration of colistin (2 MIU) in a small series of critically ill patients with pneumonia (n=12) revealed promising pharmacokinetics/pharmacodynamics results: concentrations of colistin in the epithelial lung fluid were higher than when colistimethate sodium was administered intravenously (*i.v.*) [87]. Inhaled aminoglycosides have also shown promising results in patients treated for VAP due to Gram-negative pathogens (n=16): clinical and microbiological cure were significantly higher in patients who received inhaled compared with only systemic antibiotics [88]. In a meta-analysis and systematic review including 16 studies on patients with VAP, inhaled colistin improved clinical and microbiological response, but had no effect on overall mortality in patients [89]. In another systematic review and meta-analysis including 12 RCTs or matched observational studies comparing inhaled antibiotics with *i.v.* antibiotics alone for the treatment of VAP, a higher clinical cure was observed, but no effect on microbiological cure, length of hospital stay or mortality was observed [90].

Therefore, inhaled antibiotics theoretically allow for maximisation of drug concentrations in the lungs and bronchi, and minimisation of systemic toxicity. However, there are issues that still need to be addressed. First, the efficacy of the inhaled antibiotics appears to depend on the aerosol generator and specific ventilator settings that cannot be applied to all patients [91]. Second, the choice in the antibiotic and the dosage regimens remain unclear [92]. More studies are needed to better evaluate patient outcome.

Risk of toxicity

As one strives for better pharmacodynamics target attainment, risk of toxicity may also increase. Indeed, very high levels of β-lactams may be responsible for neurotoxicity in critically ill patients [93] and high levels of vancomycin are associated with renal toxicity [94]. Therefore, the risks and benefits of increased dosage regimens must always be evaluated.

Conclusions

Delivering appropriate and adequate antibiotic therapy to the critically ill patient is quite a challenge in a world where antimicrobial resistance continues to increase and new therapeutic antibiotics remain scarce. Nevertheless, delivery of antibiotic therapy can be optimised by improving diagnostic techniques and by administering antibiotics with

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increased loading doses, prolonged or continuous infusion, or nebulisation. Routine TDM must also be considered to guide treatment to help avoid therapeutic failure and/or toxicity.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10004516

Inhaled antibiotics in chronic airway infections

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The use of inhaled antibiotics against chronic *Pseudomonas aeruginosa* infection has been a success story which has significantly contributed to the steadily improving overall survival in patients with cystic fibrosis. Suppressive inhaled antibiotic therapy has been shown to be effective with regard to improvement of clinical symptoms and quality of life. It improves lung function and slows down deterioration of lung function in the long term, while it may also decrease exacerbation frequency and prolong the time to next exacerbation. In contrast, evidence for the clinical benefits in other indications (*e.g.* bronchiectasis or NTM pulmonary disease), although promising, is still imperfect. Novel data from several clinical trial programmes on inhaled antibiotics in bronchiectasis and refractory NTM pulmonary disease will be available soon, hopefully establishing approved treatment options for these neglected conditions. In this chapter, we summarise the basic concepts, differential indications and future perspectives for the use of inhaled antibiotics in chronic airway infections.

Cite as: Ringshausen FC, Chalmers JD, Pletz MW. Inhaled antibiotics in chronic airway infections. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 57–79 [https://doi.org/10.1183/2312508X.10004616].

Historically, the targeted pulmonary application of inhaled antibiotics dates back to the 1950s, when the first attempts were made to cure patients with pneumococcal pneumonia [1]. At that time, treatment success was limited by the lack of efficient inhalation devices and nebulisers as well as side-effects due to irritating preservatives (*e.g.* phenols) contained in early formulations of inhaled antibiotics originally designated for intravenous (*i.v.*) administration. In the 1990s, major advances were made with the pivotal studies on the efficacy of tobramycin inhalation solution (TIS) in cystic fibrosis (CF) [2, 3]. Further progress has been made since then, in particular with regard to the reduction of treatment-associated burden and increase of treatment adherence with fixed drug/device combinations and easy-to-use dry powder inhalations licensed for use in CF [4, 5].

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General considerations

The administration of antibiotics by inhalation possesses striking advantages compared with the oral or *i.v.* route, including very high pulmonary drug concentrations along with comparatively low systemic toxicity due to reduced systemic absorption and reduced collateral damage (*e.g.* through resistance development in the gastrointestinal tract) [6–8]. This is a common prerequisite for the successful treatment of difficult-to-treat, often MDR and persistent pathogens, such as *Pseudomonas aeruginosa*.

However, several aspects may limit the efficacy of pulmonary deposition of inhaled antibiotics, including bronchial obstruction with viscous mucus, bacterial biofilm formation and drug-related side-effects (*e.g.* local irritation or bronchoconstriction). In addition, inhomogeneous ventilation in structurally damaged airways penalises those areas of the lungs that are affected most and would likely benefit most from targeted antimicrobial treatment [6].

Practical aspects

At present, chronic *P. aeruginosa* infection in CF remains the only indication for which inhaled antibiotics have been approved by the US Food and Drug Administration and the European Medicines Agency. However, inhaled antibiotics are often used off-label (*e.g.* in chronic *P. aeruginosa* infection in bronchiectasis, NTM pulmonary disease or chronic airway infections in lung transplant recipients). Although often consisting of established compounds without protection by patents, most of the available inhaled antibiotic agents are very costly. Thus, their long-term use puts significant economic pressure on healthcare systems. Moreover, in many countries the off-label prescription of inhaled antibiotics poses a significant financial risk for the prescribing physician (*i.e.* the risk of refund claims from health insurance companies) [9].

Therefore, as shown in table 1, inhaled antibiotics should always be accompanied by an optimised backbone treatment regimen, including identification and specific treatment of the underlying condition, smoking cessation, influenza, pertussis and pneumococcal vaccinations, pulmonary rehabilitation, and effective airway clearance techniques. Moreover, special attention should be paid to the inhalation device and/or nebuliser, inhalation technique, and hygiene measures in order to prevent recurrent infections from contaminated equipment. A suitable nebuliser should have a high aerosol output rate, including high density of nebulae and short inhalation time, a defined particle size and mass fraction <5 µm, a minimised aerosol loss to the environment, a low residual amount of the drug after nebulisation, and should be easy to clean.

Table 1. Prerequisites for the use of inhaled antibiotics

- Identification and the specific treatment of the underlying condition
- Smoking cessation
- Vaccinations against influenza, pertussis and pneumococci
- Pulmonary rehabilitation
- Effective airway clearance/chest physiotherapy
- Use of an effective inhalation device/nebuliser
- Optimal inhalation technique
- Implementation of hygiene measures

 https://doi.org/10.1183/2312508X.10004616

Hygiene measures should include cleaning after every use, disinfection in boiling water for 5 min or vaporisation at least once daily, drying for a minimum of 4 h and appropriate storage. A qualified chest physiotherapist should verify the correct inhalation technique and the implementation of hygiene measures at least once a year.

Choice of inhalation device, inhaled antibiotic and mode of administration

Some inhaled antibiotics are available as dry powder inhalations (*e.g.* ciprofloxacin, colistin, tobramycin and vancomycin) with different inhalation devices (*e.g.* T-326 inhaler (Novartis Pharmaceuticals, San Carlos, CA, USA) and Turbospin inhaler (PH&T, Milan, Italy)). In general, this mode of administration has the advantages of breath-triggered inhalation, easy handling, portability, short inhalation times and reduced risk of contamination. However, disadvantages include that inhalation is airflow dependent, thus limiting their use in very advanced stages of disease, and moreover, the potential agglutination of powders, the fact that often patients are uncertain about the efficacy of the inhalation manoeuvre and the limited line-up of available compounds.

In contrast, there are a variety of different nebulisers and nebuliser systems available for use in different patient populations, such as jet nebulisers, ultrasound nebulisers, mesh nebulisers and intermittent positive-pressure breathing devices, each with advantages and disadvantages. In general, jet and mesh nebulisers are the most widely used. Jet nebulisers generate aerosols by the use of compressors. They are efficient, robust, affordable and easy to clean, and can be used in parallel with airway clearance devices and techniques (*e.g.* PARI BOY SX; PARI, Starnberg, Germany). However, they usually require 15–20 min per inhalation session and are stationary as well as quite noisy due to the characteristic compressor unit. In contrast, mesh nebulisers generate aerosols by forcing the agent-containing liquid through a membrane (mesh) with defined porosity. Typically, they offer the same efficacy in 4–5 min in a silent and portable fashion, and thus may facilitate patient adherence (*e.g.* eFlow rapid nebuliser; PARI), although handling is often more sophisticated than in jet nebulisers. Moreover, mesh nebulisers (including their spare parts) are cost-intensive devices. Both types of nebulisers are available as "intelligent" solutions (*e.g.* with "breath-actuated nebulisation" in the AKITA JET (Vectura, Chippenham, UK) inhalation system or with "adaptive aerosol delivery" in the I-neb (Philips Healthcare, Amsterdam, the Netherlands) vibrating-mesh technology), thus potentially further improving efficacy and patient adherence.

Generally, only nebulisers and inhalation devices that have been licensed for the use of each particular inhaled antibiotic should be used. However, different devices may be chosen on an individual basis for nebulisation or inhalation. Ideally, the choice of the inhaled antibiotic should be made according to the drug's approval status, local availability, the patient's medical needs and individual preferences [10]. In real life, issues with health insurance companies often prevent necessary prescriptions of inhaled antibiotics for patients with chronic *P. aeruginosa* infection in bronchiectasis or refractory NTM pulmonary disease. In CF patients, individual preferences and adherence to therapy are often the crucial aspects for the choice of the inhaled antibiotic and its mode of delivery.

In principle, inhaled antibiotics should be used according to their approval as 28-days on/off treatment cycles or continuously. The concept of cycling inhaled antibiotics every other month goes back to the original studies of TIS and was driven initially by concerns

for resistance development in the setting of chronic antibiotic exposure [7]. However, since then, only limited data supporting this theory have emerged and the clinical relevance of the development of resistance with the use of inhaled antibiotics is still unclear [11]. If the clinical condition is critical or deteriorating despite an optimised multimodal backbone therapy, intensification of the inhaled antimicrobial treatment regimen should be considered and is commonly practised, *i.e.* the alternation of different cycled inhaled antibiotics every 28 days, *e.g.* antibiotic A followed by antibiotic B every 4 weeks, or the switch to a continuously inhaled regimen, *e.g.* colistin (with or without another cycled antibiotic, if needed) [7, 11, 12].

While healthy and well-ventilated areas of the lung achieve very high concentrations of inhaled antibiotics, concentrations are considerably lower in diseased areas with poor ventilation [6]. When comparing different modes of inhaled antimicrobial drug delivery, dry powder inhalations apparently produce higher pulmonary drug concentrations than nebulised solutions. Neither the European Committee on Antimicrobial Susceptibility Testing nor the Clinical and Laboratory Standards Institute has established breakpoints for the *in vitro* resistance testing for inhaled antibiotics. So far, only the Spanish Antibiogram Committee has proposed cut-offs for the inhalation of tobramycin, suggesting MICs $\leqslant 64\ \mu g \cdot mL^{-1}$ to represent sensitivity and MICs $\geqslant 128\ \mu g \cdot mL^{-1}$ to represent resistance for *P. aeruginosa* [13]. However, the clinical benefit of implementing these breakpoints has not yet been established, as in a Spanish study lung function improved with tobramycin inhalation in all groups regardless of the applied definition of resistance [13]. Thus, given the lack of evidence for its clinical benefit, antimicrobial resistance testing should not be used to guide therapy with inhaled antibiotics against chronic *P. aeruginosa* infection.

Monitoring of side-effects and toxicity

In general, serum levels of inhaled antibiotics are low and do not exhibit significant differences between inhalation techniques. Although they may show considerable individual variability, we do not consider regular monitoring of serum levels to be necessary. However, combined high-dose inhaled and parenteral aminoglycoside therapy should be avoided in order to reduce the risk of toxicity.

Apart from those measures stated previously in the summary of medicinal product characteristics, symptom-orientated individual monitoring of side-effects and toxicity may be implemented. In particular, this monitoring may include audiometry and laboratory parameters for renal function. In addition, supervision of the first application of a newly introduced inhaled antibiotic should be considered, in order to provide training for the correct inhalation technique and to guarantee tolerance of the novel drug or formulation. A simple approach to rule out acute bronchoconstriction is to repeat spirometry (15 and) 30 min after the first supervised inhalation of the respective inhaled antibiotic, in particular if lung function is severely impaired or if the drug is used off-label. Use of a fast-acting bronchodilator prior to administration of inhaled antibiotics should be considered in order to optimise drug delivery and reduce the risk of bronchospasm.

Management of side-effects

If clinically relevant side-effects occur after the use of an inhaled antibiotic and a fast-acting bronchodilator has already been applied beforehand, the switch to another preparation or compound should be considered. In particular, with TIS and other aminoglycosides,

 https://doi.org/10.1183/2312508X.10004616

bronchospasm, clinically striking as novel or worsening dyspnoea and/or wheezing, is frequently observed in up to one-third of patients with bronchiectasis [14, 15], while this side-effect is generally less frequently observed among patients with CF [3, 16]. Prior inhalation of a fast-acting bronchodilator may prevent bronchospasm and, therefore, is strongly recommended.

Cough is mostly observed with inhalation of dry powder antibiotics [5, 16, 17]. Thus, particular attention should be paid to the correct inhalation technique. Too fast and forceful inhalation manoeuvres lead to increased deposition of powder in the throat and thus may provoke cough. Accordingly, dry powder antibiotic formulations should be inhaled with slow but deep inspiration. If cough persists, the switch to another preparation or compound should be considered. If true allergies occur, the inhalation has to be stopped immediately and diagnostic steps should be taken in order to verify the suspected sensitisation.

Integration into the treatment schedule

In order to achieve optimal pulmonary distribution and efficacy, integration into the often-complex treatment schedule of airway clearance and inhaled medications is required. Bronchodilators, adjunct mucolytics and airway clearance techniques should be used routinely before the inhaled antibiotic is applied (figure 1).

Use of inhaled antibiotics during pregnancy and lactation

Given the fact that systematic data on the use of inhaled antibiotics in pregnancy are lacking, their routine use in expectant mothers is not recommended in some countries, *e.g.* in Germany (according to "Guideline on the management of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis pulmonary disease", Schwarz *et al.*, unpublished, currently under

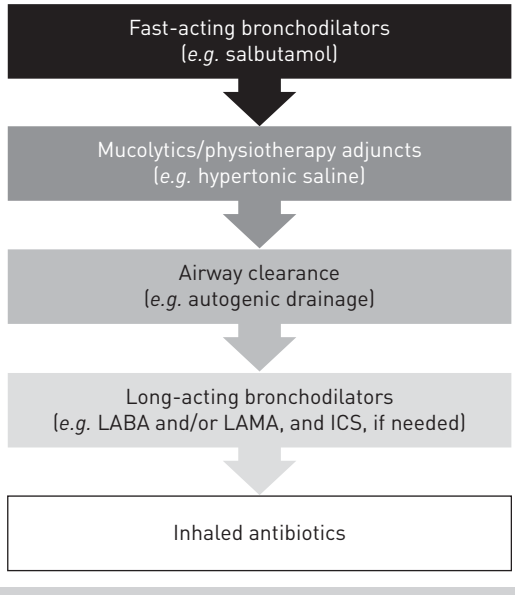

Figure 1. Hierarchy of inhaled antibiotics within a complex treatment schedule of inhaled medications, including airway clearance. LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid.

public consultation). However, there is sufficient experience from female CF patients and from *i.v.* use that may be extrapolated for some of the available compounds [18].

Inhaled low-dose aminoglycosides are unlikely to be harmful to the foetus, as absorption from the airways and lungs is low. Colistin, although also poorly absorbed, potentially passes the placental barrier. Aztreonam lysine for inhalation also crosses the placenta and should be used during pregnancy only if clearly needed.

Inhaled tobramycin and colistin should not be used during lactation due to potential ototoxicity and nephrotoxicity in the infant, while aztreonam may be used in mothers with CF. Concentrations of aztreonam in breast milk are very low after *i.v.* application and relevant enteral resorption is unlikely. Thus, the potential risks in the foetus and the infant with the use of inhaled antibiotics need to be balanced with the potential benefits or risks of refraining from inhaled antibiotics. Therefore, inhaled antibiotics may be considered according to an individual balancing of risks and benefits if the mother's clinical condition requires continued or urgent antimicrobial treatment.

Concepts and indications for inhaled antibiotics

Before initiating inhaled antibiotic therapy it is important to clarify and document the setting in which the drug is applied. Moreover, the rationale and the treatment goals should be discussed with the patient. Structured patient information sheets may assist with this process of emphasising the significance of, for example, the first *P. aeruginosa* detection in a respiratory culture with regard to the impact of chronic *P. aeruginosa* infection on the course of the disease or the reasons for treatment escalation in a rather slowly progressing condition such as NTM pulmonary disease. In the off-label setting, enforcement of an inhaled antibiotic therapy against the renitency of health insurance companies may be required. Table 2 summarises potential treatment goals for further consideration and discussion.

Eradication and sustained culture conversion

Given the irrefutable importance of *P. aeruginosa* acquisition in CF on the further course of disease, the early and aggressive treatment of the first *P. aeruginosa* detection has become

Table 2. Treatment goals for the use of inhaled antibiotics

- Pathogen eradication/sustained conversion of sputum culture ("microbiological cure")
- Pathogen suppression/reduction of bacterial load
- Radiological improvement
- Symptom control/improvement of symptoms, including reduction of infective exacerbations, amount of sputum, sputum purulence, *etc.*
- Improvement of health-related/disease-specific quality of life
- Improvement of general health status, including physical activity, body mass index, *etc.*
- Prevention or reduction of emergency consultations and admissions to hospital[#]
- Postponement or prevention of lung transplantation[#]
- Prevention of dependency from nursing care[#]
- Palliation

[#]: goals commonly shared by health insurance companies.

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an important standard of CF care [19–22]. Current evidence suggests that treatment with TIS or aztreonam lysine for inhalation solution for 28 days may achieve eradication in the vast majority of CF patients [23, 24].

In contrast, although the significance of chronic *P. aeruginosa* infection has been shown convincingly with regard to increased mortality, more extensive lung disease, worse pulmonary function as well as increased risk of exacerbations and hospitalisations [25–28], there is currently insufficient evidence to support *P. aeruginosa* eradication in subjects with bronchiectasis, mostly due to the lack of well-designed interventional studies [8].

As spontaneous clearance of *P. aeruginosa* may occur in a relevant proportion of bronchiectasis patients both in clinical practice and within RCTs [29, 30], some authors will obtain a second confirmatory sputum sample before initiating eradication therapy [8].

In NTM pulmonary disease, eradication of mycobacteria (*i.e.* sustained culture conversion for >12 months after cessation of antimycobacterial combination therapy) is an important treatment goal, which correlates well with other markers of clinical treatment success. Inhaled amikacin recently gained attention in refractory NTM pulmonary disease due to MAC and *Mycobacterium abscessus* complex (MABSC), and is currently being investigated as an emerging additional treatment option [31, 32]. However, sustained culture conversion may only be achievable in a minority of patients, thus often requiring adaptation of the treatment goal.

Treatment of pulmonary exacerbations

The treatment of pulmonary exacerbations is usually event driven, *i.e.* is commenced with clinical worsening, typically due to a respiratory infection. The decision to initiate treatment is taken *ad hoc*, utilising oral or *i.v.* antibiotics, without respect for previous (cycles of) inhaled antibiotics.

However, mild infective pulmonary exacerbations of CF or bronchiectasis not requiring hospitalisation or *i.v.* antimicrobial treatment may be treated sufficiently with inhaled antibiotics, if necessary in combination with oral antipseudomonal antibiotics (*e.g.* ciprofloxacin or levofloxacin) [33]. Combinations of parenteral antipseudomonal antibiotics and inhaled antibiotics are commonly avoided in CF and bronchiectasis given the lack of evidence for a clinical benefit and the potentially increased risk of toxicity, in particular if the same drug class is used. However, evidence emerged recently in VAP suggesting that combined *i.v.* and aerosolised treatment may have additional benefits, but no higher nephrotoxicity [34].

Chronic bacterial suppression

The intention behind suppressive therapy is to contain chronic infection, to reduce associated airway inflammation, and to prevent or postpone the structural damage to the airways and the pulmonary parenchyma [35]. Initiation of suppressive therapy may be considered if the target pathogen is persistently cultured from respiratory samples, if the patient is clinically deteriorating or at risk for deterioration and if eradication could not be achieved. In chronic *P. aeruginosa* infection oral (quinolones), *i.v.* (a combination of two active drugs, typically

applied for 14 days in intervals of 3–4 months) and inhaled antibiotics (continuously or cycling on/off every month) or their combinations are applied (in sequence) for suppressive therapy on an individual basis. Of note, although widely practised, the evidence for the effectiveness of suppressive elective *i.v.* antibiotic therapy in CF patients is low [36].

The rationale for using suppressive therapy in CF and bronchiectasis is to tackle the sequelae of chronic *P. aeruginosa* infection. In CF patients, suppressive therapy has been proven effective, reducing bacterial load and preventing progressive worsening of lung function and pulmonary exacerbations [5, 12, 16, 37–48]. However, it remains unclear how bacterial load and lung function correlate and interact in the further course of disease, in particular as the CF airway microbiome appears to be stable over time [49].

In CF and bronchiectasis, suppressive therapy with inhaled antibiotics is indicated for chronic *P. aeruginosa* infection of the lower airways. However, its efficacy depends on the mode of antibiotic drug delivery, with varying evidence for CF and bronchiectasis. In refractory NTM pulmonary disease, suppressive inhaled antibiotic therapy with off-label amikacin may improve symptom control in the long term [32].

Established indications for the use of inhaled antibiotics include chronic *P. aeruginosa* infection in CF and bronchiectasis as well as refractory NTM pulmonary disease. The following sections will provide further details on specific aspects regarding the differential use in these indications. In addition, inhaled antimicrobial agents are used in VAP, chronic MRSA airway infection, chronic airway infections in subjects with COPD, and chronic bacterial and fungal airway infections in CF and non-CF lung transplant recipients. However, it needs to be noted that, currently, inhaled antibiotics are only approved for use against chronic *P. aeruginosa* infection in CF patients [7, 8].

Chronic *P. aeruginosa* infection in CF

Chronic airway infection by *P. aeruginosa* is of critical importance for the further course of the patient with CF. Accordingly, the suppressive use of inhaled antibiotics against chronic *P. aeruginosa* infection has been a success story and has significantly contributed to the steadily improving overall survival in subjects with CF [50, 51]. Of note, there is considerable variation regarding the underlying definition of chronic *P. aeruginosa* infection among the clinical trials that established the efficacy of suppressive therapy. However, a consistent definition of chronic *P. aeruginosa* infection is crucial. According to the EuroCareCF Working Group, chronic *P. aeruginosa* infection of the lower airways is present if more than half of the airway culture samples (spontaneous sputum, induced sputum, deep throat swab, BAL) within 1 year are positive for *P. aeruginosa*, given that at least six samples have been taken and were equally distributed throughout the year. If the patient is known to be chronically infected by *P. aeruginosa* based on *P. aeruginosa* antibody titres and/or positive culture results from previous years, a minimum of four bacteriological samples is considered sufficient [52, 53]. However, *P. aeruginosa* antibodies are used inconsistently between different age groups, countries and settings.

Suppressive therapy of chronic *P. aeruginosa* infection has been shown to be effective in CF with regard to improvement of clinical symptoms, including reduction of the sputum volume and purulence in accordance with the reduction in bacterial load [5, 12, 16, 37–44], weight gain [37, 41, 45], reduction in loss of productivity [37], and reduction of

 https://doi.org/10.1183/2312508X.10004616

i.v. antipseudomonal antibiotic use [37, 42]. Moreover, recent contributions to the field established evidence for the improvement of health-related quality of life, as measured by appropriate questionnaires (*e.g.* the Cystic Fibrosis Questionnaire Revised), as well as patient satisfaction with inhaled antibiotic therapies [5, 16, 40–43]. Consistently, within clinical trials, inhaled suppressive therapy led to an improvement of lung function, to a deceleration of lung function decline as well as to a reduction in exacerbation frequency and prolongation of the time to next exacerbation [5, 16, 37–40, 42, 43, 45–48]. Thus, a positive impact on overall survival may be reasoned. However, direct evidence for the reduction of mortality in CF from large RCTs that observed patients over an extended period of time is lacking. In 2011, a systematic Cochrane review on the efficacy of long-term application of inhaled antibiotics in CF concluded that inhaled antibiotics probably result in an improvement of lung function and in a reduction of the exacerbation rate, with the best evidence available at that time for TIS [54]. However, the low number of study subjects, significant heterogeneity and poor data quality of the included randomised trials hampered pooled meta-analysis. Most clinical trials were limited to up to 6 months of inhaled antibiotic therapy. Thus, evidence for the efficacy and the clinical benefits (including the reduction of mortality) of long-term application is lacking. In 2012, Sawicki *et al.* [55] presented data on 12 740 patients included in the US Cystic Fibrosis Foundation's Patient Registry, suggesting that use of TIS was associated with a significantly improved overall survival.

Of note, although commonly applied in countries such as the UK and Germany, the use of nebulised colistin against chronic *P. aeruginosa* infection in CF is not supported by clinical trials of sufficient quality [56, 57]. As the available inhaled antibiotics possess differential properties, and as comparability between compounds and products is limited, the choice of the appropriate inhaled antibiotic should be made on an individual basis considering patient-associated aspects [7, 57, 58].

Table 3 shows the variety of currently available inhaled antibiotic agents and products that are licensed for the routine use in CF with chronic *P. aeruginosa* infection in Germany, including recommended nebulisers and appropriate drug doses for application. Recently, the quinolone levofloxacin was approved by the European Medicines Agency as another drug class for use as an inhaled antibiotic [46, 62]. The approval of liposomal amikacin for inhalation (LAI) for chronic *P. aeruginosa* infection in CF is expected in the near future [43, 63]. In addition, further compounds are currently being developed for use as inhaled antibiotics [64, 65].

Chronic *P. aeruginosa* infection in bronchiectasis

In contrast to the situation in CF, where a variety of approved treatment options exist, allowing tailoring inhaled antibiotic therapy according to medical needs and patient preferences [10, 58], no inhaled antibiotics have been approved in other disease areas, including bronchiectasis. Obviously, the burden of bronchiectasis is steadily and globally increasing [66–69], emphasising the urgent need for effective therapies in bronchiectasis [70].

The rationale for using inhaled antibiotics in bronchiectasis is similar to that in CF. However, definitions of chronic *P. aeruginosa* infection are even less consistent and less strict in bronchiectasis, typically requiring two or more *P. aeruginosa* detections from airway cultures when clinically stable within the past year [71].

Table 3. Inhaled antibiotics licensed for use in chronic *Pseudomonas aeruginosa* infection in cystic fibrosis in Germany[#]

Agent	Product	Company	Mode and volume of application	Single dose	Application interval and cycle	Nebuliser/ inhalation device	Age group years
Tobramycin	Vantobra	PARI (Starnberg, Germany)	Inhalation solution (1.7 mL ampoule)	170 mg	Twice daily (every 12 h), 28 days on/off	Tolero/eFlow rapid[¶]	6+
	TOBI	Novartis (Nürnberg, Germany)	Inhalation solution (5 mL ampoule)	300 mg	Twice daily (every 12 h), 28 days on/off	PARI LC Plus; eFlow rapid[+]	6+
	Tobramycin TEVA	TEVA (Ulm, Germany)	Inhalation solution (5 mL ampoule)	300 mg	Twice daily (every 12 h), 28 days on/off	PARI LC Plus; eFlow rapid[+]	6+
	TOBI Podhaler	Novartis	Capsules with dry powder, 28 mg each	112 mg	Twice daily (every 12 h), 28 days on/off	Podhaler (T-326 dry powder inhalation device)[¶]	6+
	Gernebcin 40 mg·1 mL^{-1}	InfectoPharm (Heppenheim, Germany)	Inhalation solution (1 mL ampoule)	40 mg	Twice daily, continuously	*e.g.* PARI LC Sprint	All, recommended for children <10 years
	Gernebcin 80 mg·2 mL^{-1}	InfectoPharm	Inhalation solution (2 mL ampoule)	80 mg	Twice daily, continuously	*e.g.* PARI LC Sprint	All, recommended for children ⩾10 years
	Gernebcin 160 mg·2 mL^{-1}	InfectoPharm	Inhalation solution (2 mL ampoule)	160 mg	Twice daily, continuously	*e.g.* PARI LC Sprint	All, recommended for children ⩾10 years

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Table 3. Continued

Agent	Product	Company	Mode and volume of application	Single dose	Application interval and cycle	Nebuliser/ inhalation device	Age group years
	Bramitob	Chiesi (Hamburg, Germany)	Inhalation solution (4 mL ampoule)	300 mg	Twice daily (every 12 h), 28 days on/off	PARI LC Plus/ PARI TurboBOY or PARI LC Sprint/PARI TurboBOY SX	6+
Colistin (colistimethate sodium)	ColiFin 1 MIU	PARI	Powder and solvent for an inhalation solution (+3 mL NaCl 0.9%)	80 mg (1 MIU)	⩾2 years: 1–2 MIU twice daily (maximum 6 MIU·day^{-1}), continuously; <2 years: 0.5–1 MIU twice daily (maximum 2 MIU·day^{-1}), continuously	⩾2 years: eFlow rapid; <2 years: PARI LC Sprint Baby recommended	All
	ColiFin 2 MIU	PARI	Powder and solvent for an inhalation solution (+4 mL NaCl 0.9%)	160 mg (2 MIU)	⩾2 years: 1–2 MIU twice daily (maximum 6 MIU·day^{-1}), continuously; <2 years: 0.5–1 MIU twice daily (maximum 2 MIU·day^{-1}), continuously	⩾2 years: eFlow rapid; <2 years: PARI LC Sprint Baby recommended	All
	Colistin CF	Forest (Utrecht, the Netherlands)	Powder and solvent for an inhalation solution (+3 mL NaCl 0.9%)	80 mg (1 MIU)	⩾2 years: 1–2 MIU twice daily (maximum 6 MIU·day^{-1}), continuously; <2 years: 0.5–1 MIU twice daily (maximum 2 MIU·day^{-1}), continuously	PARI LC Plus, PARI LC Star, eFlow rapid	All

Continued

Table 3. Continued

Agent	Product	Company	Mode and volume of application	Single dose	Application interval and cycle	Nebuliser/ inhalation device	Age group years
	Colistineb	Forest	Powder and solvent for an inhalation solution (+3 mL NaCl 0.9%)	80 mg (1 MIU)	⩾2 years: 1–2 MIU twice daily (maximum 6 MIU·day^{-1}), continuously; <2 years: 0.5–1 MIU twice daily (maximum 2 MIU·day^{-1}), continuously	PARI LC Plus, PARI LC Star, eFlow rapid	All
	Colistineb	Forest	Powder and solvent for an inhalation solution (+4 mL NaCl 0.9%)	160 mg (2 MIU)	⩾2 years: 1–2 MIU twice daily (maximum 6 MIU·day^{-1}), continuously; <2 years: 0.5–1 MIU twice daily (maximum 2 MIU·day^{-1}), continuously	PARI LC Plus, PARI LC Star, eFlow rapid	All
	Colobreathe	Forest (Barnstaple, UK)/ Teva (Haarlem, the Netherlands)	Capsules with dry powder, 125 mg each	125 mg (1.66 MIU)	Twice daily (every 12 h), continuously	Turbospin dry powder inhalation device[¶]	6+
	Promixin	Profile (Chichester, UK)/ Zambon (Planegg/ Martinsried, Germany)	Powder and solvent for an inhalation solution (+1–3 mL water for injection or water for injection/NaCl 0.9%)	80 mg (1 MIU)	⩾2 years: 1–2 MIU twice daily (maximum 6 MIU·day^{-1}), continuously; <2 years: 0.5–1 MIU twice daily (maximum 2 MIU·day^{-1}), continuously	I-neb adaptive aerosol delivery system[¶], PARI LC Plus	All

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Table 3. Continued

Agent	Product	Company	Mode and volume of application	Single dose	Application interval and cycle	Nebuliser/ inhalation device	Age group years
Aztreonam	Cayston	Gilead (Cambridge, UK)	Powder and solvent for an inhalation solution	75 mg	Three times daily (minimum interval 4 h), 28 days on/off	Altera/eFlow rapid[¶]	6+
Levofloxacin	Quinsair	Raptor (Amsterdam, the Netherlands)	Inhalation solution (2.4 mL ampoule)	240 mg	Twice daily (every 12 h), 28 days on/off	Zirela/eFlow rapid[¶]	18+

[#]: note that country-specific approval status may exist for some drugs; [¶]: fixed drug/device combinations; [+]: nebulisation with an eFlow rapid may be considered as an alternative for nebulisation with a PARI LC Plus [59–61].

https://doi.org/10.1183/2312508X.10004616

Recently, unambiguous evidence was reported for the significance of chronic *P. aeruginosa* infection in bronchiectasis, demonstrating that *P. aeruginosa* is associated with a 3-fold increased risk of death as well as an increase in hospital admissions and exacerbations [26]. However, several attempts to extrapolate the evidence for the use of inhaled antibiotics from CF to bronchiectasis have been unsuccessful, with no compound licensed so far. The reasons why commercial studies failed to demonstrate clinical benefits and missed their primary end-points are in part related to adverse events [14, 72] and to difficulties in study designs. Apparently, patients enrolled in RCTs in bronchiectasis appear to be only partially representative of patients in clinical practice [73].

However, a noncommercial investigator-initiated single-blind controlled trial of continuously nebulised gentamicin over a 1-year period demonstrated significant clinical benefits, including a reduction of bacterial density, a higher rate of pathogen eradication, an improvement of quality of life and reduced exacerbations [15]. The results of this important trial offer an effective alternative for clinical practice with an acceptable cost–performance ratio compared with the high-priced inhaled antibiotics currently licensed for use in CF patients. As outlined in table 4, inhaled aztreonam was associated with an increased rate of adverse events in patients with bronchiectasis, in contrast to successful studies in CF patients [72]. Therefore, aztreonam has not been licensed in bronchiectasis.

A recent systematic review on inhaled antibiotics (amikacin, aztreonam, ciprofloxacin, gentamicin, colistin or tobramycin) for stable bronchiectasis with chronic bronchial infection including eight trials on 590 patients found that inhaled antibiotics effectively reduced sputum bacterial load, eradicated bacteria from sputum and reduced the risk of acute exacerbations [81]. Bronchospasm occurred in 10% of patients. The authors of the review concluded that inhaled antibiotics represent an effective suppressive therapy with an acceptable safety profile in adult patients with stable bronchiectasis [81].

Table 4 summarises the current state of development for inhaled antibiotics in bronchiectasis. Of note, the first results from a phase III double-blind RCT on ciprofloxacin dry powder for inhalation over a 48-week period for non-CF bronchiectasis (RESPIRE 1) recently became available [77], demonstrating a significant prolongation of the time to first exacerbation and a reduction of the exacerbation frequency by 39% in the 14-days on/off treatment group. This trial included patients with *P. aeruginosa* as well as other ciprofloxacin-sensitive bacteria. Interestingly, these effects were not seen in the 28-days on/off treatment group. The results from the parallel study RESPIRE 2 are expected soon. The results from two phase III double-blind randomised controlled parallel trials on once-daily dual-release liposomal ciprofloxacin (ORBIT-3 and ORBIT-4) were also recently reported in a preliminary form [79]: while ORBIT-4 reached its primary and key secondary end-point to increase the median time to first pulmonary exacerbation and to reduce the frequency of pulmonary exacerbations, respectively, ORBIT-3 failed in this respect. However, the combined data indicated a significant 27% reduction in pulmonary exacerbations. Currently, several clinical trial programmes are being launched for inhaled antibiotics in bronchiectasis, including colistin (phase III) and tobramycin inhalation powder (phase II), giving reason to expect exciting times in bronchiectasis.

Refractory NTM pulmonary disease

Recently, with the steadily increasing burden of disease [68, 82, 83], interest in inhaled antibiotic agents has arisen regarding the treatment of NTM pulmonary disease caused by

 https://doi.org/10.1183/2312508X.10004616

Table 4. Current evidence for inhaled antibiotics for bronchiectasis

Agent [ref.]	Patients n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
Amoxicillin [74–76]	6 [74], 3 [75], 5 [76]	Three open-label studies following failure of oral antibiotics	Sputum purulence	Continuous; 4 months/ 16 weeks	Bronchiectasis patients with purulent sputum that failed to clear following oral amoxicillin	Reduced sputum purulence; reduced neutrophil elastase activity; reduced sputum volume; improved peak expiratory low rate	No issues identified
Tobramycin [14]	Active 37, placebo 37	Phase II study	*P. aeruginosa* bacterial load	28 days treatment (total duration 8 weeks)	*P. aeruginosa*-colonised patients; mean age 66 *versus* 63 years; FEV_1 % pred mean 56% *versus* 53%	Significant reduction in *P. aeruginosa* load (mean difference 4.56 $\log_{10}CFU{\cdot}mL^{-1}$; p<0.01); 13 out of 37 cleared *P. aeruginosa* from sputum; no significant change in FEV_1 (p=0.41)	Increased dyspnoea, chest pain and wheezing; new resistance to tobramycin in 4 out of 36
Gentamicin [15]	Active 27, placebo 30	Single-blind RCT	Bacterial load	12 months	Patients colonised with any pathogens in at least three sputum samples in the preceding 12 months; ⩾2 exacerbations in the previous year; able to tolerate test dose of gentamicin; FEV_1 % pred >30%; ex-smokers of >1 year; not on long-term antibiotics	Significant difference in bacterial load at 12 months (2.96 *versus* 7.67 $\log_{10}CFU{\cdot}mL^{-1}$; p<0.0001); reduction in exacerbations (median 0 in the gentamicin group, 1.5 in the saline group; p<0.0001); improved SGRQ and Leicester Cough Questionnaire scores; reduced airway inflammation	Bronchospasm in 22%, two withdrawals; elevated serum gentamicin levels required dose reduction in one patient; no resistant isolates detected

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Table 4. Continued

Agent [ref.]	Patients n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
Colistin [71]	Active 73, placebo 71	Phase III double-blind RCT	Time to first exacerbation	6 months (patients withdrawn following exacerbation)	*P. aeruginosa*-colonised patients (⩾2 positive cultures in 12 months) and within 21 days of completing antipseudomonal antibiotics for an exacerbation	Missed primary end-point (colistin 165 days, placebo 111 days; p=0.11); improved SGRQ (mean difference −10.5 points; p=0.006); improved time to first exacerbation in patients taking >80% of doses	Five patients (7%) developed bronchoconstriction leading to discontinuation; no resistant strains at follow-up
Aztreonam [72]	AIR-BX1: active 134, placebo 132; AIR-BX2: active 136, placebo 138	Two phase III double-blind RCTs	QoL-B questionnaire score at week 4	Two 28-day treatment courses with alternating 28 day off treatment	Positive sputum for *P. aeruginosa* or other Gram-negative organisms (excluding *Haemophilus influenzae*); FEV_1 % pred >20%; chronic sputum production	No difference in QoL-B at week 4 (mean difference 0.8 (95% CI −3.1–4.7; p=0.7) in AIR-BX1 and 4.6 (95% CI −3.1–4.7; p=0.011) in AIR-BX2); no difference in QoL-B in both studies at week 12 (p=0.56 in both studies); no difference in time to first exacerbation	AIR-BX1 adverse events leading to discontinuation 22% *versus* 6%; AIR-BX2: adverse events leading to discontinuation 10% *versus* 5%
Ciprofloxacin DPI [77, 78]	Active 60, placebo 64	Phase II double-blind RCT	Bacterial load	28 days treatment with follow-up to 84 days	Idiopathic or post-infective bronchiectasis; ⩾2 exacerbations in the previous 12 months (one hospitalisation); able to produce sputum; culture positive for target microorganisms	Mean difference in bacterial load −3.62 *versus* −0.27 $\log_{10}$ CFU·mL^{-1} (p<0.001); no significant differences in proportion of patients with exacerbations (37% *versus* 39.1%; p=0.6); no significant difference in SGRQ (mean difference −3.56; p=0.059)	10% of patients developed resistance (MIC >4 mg·L^{-1}) in the ciprofloxacin group; no difference in adverse events between groups

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Table 4. Continued

Agent [ref.]	Patients n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
	RESPIRE 1[#]: active 14 days 137, placebo 14 days 68; active 28 days 141, placebo 28 days 70	Phase III double-blind RCT	Time to first exacerbation *versus* pooled placebo and frequency of exacerbation *versus* matched placebo	48 weeks, 14-days and 28-days on/off treatment regimens	Idiopathic or post-infectious bronchiectasis; ⩾2 exacerbations in the previous 12 months; FEV_1 % pred ⩾30%; positive sputum culture at screening for *P. aeruginosa* or target microorganisms	Ciprofloxacin DPI 14-days on/off reduced frequency of exacerbations by 39% over 48 weeks and significantly reduced the time to first exacerbation; the 28-days on/off regimen had no significant effect for either end-point	Frequency of treatment emergent adverse events was similar across groups; any serious adverse event 20% in 14-days on/off, 23% in 28-days on/off and 27% in placebo group
Liposomal ciprofloxacin [79, 80]	Active 20, placebo 22	Phase II study double-blind RCT	Bacterial load after first 28-day treatment cycle with intervening 28-day off periods	24 weeks (three 28-day treatment cycles)	*P. aeruginosa*-colonised patients; >2 exacerbations in previous 12 months	Reduction in *P. aeruginosa* bacterial load −4.2 *versus* -0.08 $\log_{10}CFU{\cdot}mL^{-1}$ (p=0.002); reduced number of exacerbations in the active treatment group (odds ratio 0.2, 95% CI 0.04–0.89; p=0.027); median time to PEs reduced in the per-protocol population (p=0.046)	No significant difference in MICs to ciprofloxacin at day 28; no increase in adverse events

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Table 4. Continued

Agent [ref.]	Patients n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
	Not reported yet[¶]	Two phase III double-blind RCTs (ORBIT-3/-4)	Increase in median time to first PE; secondary end-point: frequency of PEs	48-week double-blind treatment period	Adult bronchiectasis; ⩾2 exacerbations in the previous 12 months; chronically *P. aeruginosa*-infected	ORBIT-3: median time to PE 221 days in treatment group *versus* 136 days in placebo group (p=0.85), 13% reduction in PEs (p=0.3125); ORBIT-4: median time to PE 230 days in treatment group *versus* 163 days in placebo group (p=0.046), 37% reduction in PEs (p=0.0007); combined data: 27% reduction in PEs (p=0.002)	Frequency of treatment emergent adverse events was similar across groups

P. aeruginosa: *Pseudomonas aeruginosa*; FEV_1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; QoL-B: Quality of Life-Bronchiectasis; DPI: dry powder for inhalation; PE: pulmonary exacerbation. [#]: results from the parallel study RESPIRE 2 (ClinicalTrials.gov, trial number NCT02106832) are pending at the time of writing this chapter; [¶]: results from the two phase III double-blind randomised controlled parallel trials ORBIT-3 and ORBIT-4 have recently been reported in a preliminary form [79]. Reproduced and modified from [8] with permission.

https://doi.org/10.1183/2312508X.10004616

MAC and MABSC, which represent further difficult-to-treat and naturally MDR microorganisms.

In a small retrospective study of 20 subjects, inhaled amikacin added to an ongoing regimen in patients with treatment-refractory MAC pulmonary disease or MABSC pulmonary disease was shown to achieve microbiological and symptomatic improvement in a significant number of patients [32]. However, toxicity (including ototoxicity, nephrotoxicity and haemoptysis) resulted in treatment discontinuation in 35% of patients [32].

LAI is a once-daily formulation of amikacin with extended drug release, which is currently in development for treatment of refractory NTM pulmonary disease. LAI possesses a mechanism of action that may lower the risk of the aminoglycoside-related systemic toxicity and improve clinical outcomes. Pre-clinical studies show that LAI delivers a targeted, high concentration of amikacin into the lungs, and that the liposomes penetrate the membranes of the airway submucosa and macrophages where NTM reside and proliferate [84, 85]. Very recently, results from a randomised placebo-controlled open-label study in patients with refractory NTM pulmonary disease were published [31]. Although the primary end-point, *i.e.* change from baseline to day 84 on a semiquantitative mycobacterial growth scale, was missed, the findings suggest that once-daily LAI added to standard-of-care therapy for at least 84 days can yield significant improvements in culture negativity rates (from 9% in the placebo arm to 32% in the treatment arm) and physical activity as measured by distance walked in the 6-min walk test [31]. However, in this trial the treatment effect was predominantly in non-CF patients with MAC and was sustained for 1 year beyond the use of LAI. Most adverse events were respiratory in nature and led to drug discontinuation in some patient. Currently, an open-label phase III global trial evaluating the safety and efficacy of LAI in patients with refractory MAC pulmonary disease is ongoing (CONVERT (Study to evaluate efficacy of LAI when added to multidrug regimen compared to multidrug regimen alone); ClinicalTrials.gov, trial number NCT02344004).

Other chronic airway infections

The use of inhaled antibiotics in chronic *P. aeruginosa* infections in CF acts as a successful role model for the off-label use of inhaled antibiotics for other settings and key pathogens involved in chronic airway infections, such as chronic non-*P. aeruginosa* infection in bronchiectasis, chronic *Aspergillus* infection after lung transplant or persistent MRSA infection in CF [86].

As an example, two recent studies with nebulised gentamicin and inhaled ciprofloxacin powder for inhalation demonstrated clinical benefits in subjects chronically infected with susceptible pathogens such as *Haemophilus influenzae* or *S. aureus* [15, 78].

A US multicentre phase II double-blind RCT of vancomycin inhalation powder for the treatment of persistent MRSA lung infection in CF patients demonstrated that study participants who received vancomycin inhalation powder experienced a significant reduction in sputum MRSA density compared with placebo (Efficacy and safety study of AeroVanc for the treatment of persistent MRSA lung infection in cystic fibrosis patients; ClinicalTrials.gov, trial number NCT01746095).

In summary, further research is urgently needed, as current evidence is too limited to support the routine use of inhaled antibiotics in chronic airway infections of microbial origin other than *P. aeruginosa*.

Encapsulation of inhaled antibiotics

Encapsulation of inhaled antibiotics is a dynamic research field offering fascinating possibilities to increase the clinical efficacy of compounds. Encapsulation can decrease toxicity, increase pulmonary drug deposition by enhanced mucus penetration, targeted release and increased stability, and may even potentate antimicrobial efficacy, particularly in biofilms. Carriers under investigation include liposomes and polymeric biodegradable nanoparticles. Liposomal bilayers have been shown to fuse with the plasma membranes of eukaryotic and bacterial cells, and thus enable intracellular deposition of the encapsulated therapeutics, which is of particular interest for treatment of infections by intracellular bacteria, such as *Mycobacterium* spp. or intracellularly hidden *S. aureus* variants, or in improving the antibiotic deposition in metabolically inactive persisters in bacterial biofilms.

Although polymeric nanoparticles possess the advantages of higher physicochemical stability, more modified surface properties, and prolonged drug delivery and shelf-life compared with liposomes, only a few polymeric encapsulated antibiotics have emerged recently in the context of pulmonary drug delivery. Polymers based on organic compounds, such as poly(lactic acid), poly(sebacic acid) and poly(lactic-*co*-glycolic acid) (PLGA), show excellent biodegradability and biocompatibility, with PLGA being the most intensively investigated polymeric drug delivery system for different pulmonary applications. Most of these studies were performed *in vitro*; *in vivo* applications are still rare [6].

Conclusions

While inhaled antibiotics already have proven impressive efficacy in the long-term suppressive therapy of chronic *P. aeruginosa* infection CF, evidence for the clinical benefits in other indications is still imperfect. Data from several clinical trials in bronchiectasis and refractory NTM pulmonary disease will be available soon, hopefully establishing approved treatment options for these neglected and under-researched conditions. Fortunately, novel targets for inhaled antibiotics in neglected chronic airway infections are currently in development. Furthermore, encapsulation of inhaled antibiotics into liposomes or nanoparticles may decrease toxicity, and increase mucus penetration and antimicrobial efficacy, even in biofilms.

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Disclosures: F.C. Ringshausen has received grants from Bayer Healthcare, Grifols and Insmed. He has also received personal fees and other fees in support of patient educational events from Abbott, AstraZeneca, Bayer Healthcare, Brahms/Thermo Fisher Scientific, Cellestis/Qiagen, Chiesi, Forest, Grifols, Insmed, Gilead, Heinen & Löwenstein, MSD, Novartis, Oxycare, Pfizer and InfectoPharm. J.D. Chalmers has received grants from Aradigm, AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, GSK, Novartis and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, Chiesi, Napp and Pfizer. M.W. Pletz has received grants from the German Research Foundation, the German Ministry for Science and Education, Biotest, InfectoPharm and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Biotest, Clinigen, InfectoPharm, MSD, Pfizer and Thermo Fisher, and has a patent "Measuring antibiotic blood levels with Raman spectroscopy" pending.

Chapter 5

Inhaled antibiotics in critical care

Charles-Edouard Luyt and Jean Chastre

Antibiotic aerosolisation in patients with VAP has received renewed interest with the recent development of a new generation of nebulisers that use a vibrating mesh. These devices allow very high concentrations of antimicrobial agents to be achieved in the deep compartment of the lung, well above those achievable using the intravenous route. However, data in critically ill patients with pneumonia are limited; most of the reported experiences are case reports, descriptive studies or literature reviews. According to the systematic reviews and meta-analyses, administration of aerosolised antibiotics might increase the likelihood of clinical resolution (particularly in VAP caused by resistant pathogens), but this is not translated consistently into a significant improvement of important outcomes such as mortality or mechanical ventilation duration. Thus, despite recent promising findings, the widespread use of aerosolised antibiotics to treat pneumonia in the ICU setting cannot be recommended. It should be restricted to the treatment of XDR Gram-negative pneumonia. In these cases, the use of a vibrating-mesh nebuliser seems to be more efficient.

Cite as: Luyt C-E, Chastre J. Inhaled antibiotics in critical care. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 80–96 [https://doi.org/10.1183/2312508X.10004716].

Aerosol antibiotic administration allows high drug concentrations at the infection site with, at least theoretically, low systemic absorption. This may decrease toxicity, particularly the renal toxicity of aminoglycosides and colistin. Whereas antibiotic aerosolisation is part of routine practice in children with cystic fibrosis [1, 2], data are scarce for patients on mechanical ventilation. Until recently, development of this technique was slow, partly due to the limited knowledge of the determinants of aerosolisation during mechanical ventilation and poor technique implementation. Large amounts of particles are dispersed by conventional nebulisers and remain trapped in the ventilatory circuits and the tracheobronchial tree, therefore not reaching the distal lung, and hence lower amounts of drug are available in the alveolar compartment. With the development of the latest generation of nebulisers [3–7], antibiotic aerosolisation in patients with VAP has received renewed interest [8–10].

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Rationale for the use of inhaled antibiotics in mechanically ventilated patients

There are several good reasons for the use of inhaled antibiotics. The most important is the pharmacokinetics/pharmacodynamics of antibiotics in critical care patients: the variability is well known [11] and thus giving antibiotics directly to the site of infection seems to be, at least theoretically, better than intravenous (*i.v.*) administration. It avoids dilution of the drug in a very large volume of distribution, rapid metabolism or urinary excretion [11–13]. Other reasons include the following.

First, the frequency of VAP caused by MDR pathogens has increased in recent years and will continue to do so [14]. For these strains, particularly for Gram-negative MDR bacilli, MICs of still-active antibiotics, mainly aminoglycosides, are higher, very close to the breakpoint defining the potential efficacy of these antibiotics. To treat these strains, raising the dose of systemic antibiotic can be responsible for an increased toxicity and lead to acute renal failure. Nebulisation offers the advantage of high local doses without systemic accumulation [8, 15–17].

Second, lung penetration of antibiotics infused *i.v.* is poor, in particular for aminoglycosides. For example, the coefficient of lung penetration of tobramycin and gentamicin is between 10% and 30% after a single *i.v.* infusion [18–20]. The objective of direct antibiotic delivery to the lower airways is to obtain a high drug concentration, at the parenchymal level, while the blood level remains low, thus avoiding or limiting toxicity [16].

Third, although never demonstrated, nebulisation is probably better than tracheal instillation (another method to deliver antibiotics to the lower airways). While tracheal instillation obtains high antibiotic concentrations in the tracheal secretions [21], the exact diffusion in the distal airways and the alveolar compartment is not known. Moreover, the distribution of the drug in the lungs most probably depends on gravity and the severity of the parenchymal lesions, and thus could be very heterogeneous. This limitation of tracheal instillation is at least partially overcome by the use nebulisation, in particular with newer devices [22].

Last, microflora of the gut is probably less altered with nebulised antibiotics than with systemic antibiotics, which might decrease the emergence and dissemination of resistant strains, including *Clostridium difficile* [15].

Animal data supporting the superiority of nebulisation over *i.v.* administration

Several studies in animal models of VAP have shown that antibiotic nebulisation leads to high antibiotic concentrations into the lung, higher than after *i.v.* infusion. In healthy piglets, Goldstein *et al.* [23] compared amikacin lung tissue concentrations after nebulisation (using an ultrasonic nebuliser) to those after *i.v.* administration. The lung concentrations of amikacin were more than 10-fold higher after nebulisation than the lung concentrations after *i.v.* administration and were homogeneously distributed throughout the lung parenchyma. These concentrations were far above the MIC of most Gram-negative

strains responsible for VAP [23]. These data were confirmed in piglets with experimental pneumonia due to *Escherichia coli*: the amikacin lung concentration was 3–30-fold higher after nebulisation than after *i.v.* administration [24]. In the piglets that received nebulised amikacin, lung amikacin concentrations were lower in the infected (consolidated) lung than in the noninfected (nonconsolidated) lung, but even in the infected parenchyma the concentration was higher than that achieved with *i.v.* amikacin. Moreover, bactericidal efficacy was better after nebulisation than after *i.v.* administration: the lung bacterial burden was significantly lower in the animals receiving nebulised amikacin than in the animals receiving amikacin *i.v.* [24].

Recently, lung deposition of colistin administered *i.v.* or *via* a vibrating-mesh nebuliser was evaluated in piglets by the same team [25]. In that study, colistin was undetected in lung tissue following *i.v.* infusion, whereas it was detected in the lung parenchyma of animals receiving nebulised colistin, with peak lung tissue concentrations greater in lung segments with mild pneumonia than in lung segments with severe pneumonia. Accordingly, the bacterial burden in the lungs of aerosol-treated animals was lower than in the lung of *i.v.*-treated animals [25].

Clinical studies supporting the use of nebulised antibiotics

One of the main limitations to the use of nebulised antibiotics to treat VAP is that only a few of them are available for human use. For example, in France, specific formulations for nebulisation are available only for colistin and tobramycin; whereas in the USA, none of these drugs have been approved by the US Food and Drug Administration for nebulisation and no specific formulation exists to date. Most published studies evaluated aminoglycosides and colistin use. A recent meta-analysis suggested that nebulised antibiotics could be beneficial in patients with VAP; however, the conclusions were limited due to the small number and heterogeneity of the studies included [26].

Aminoglycosides nebulisation

In 1993, Le Conte *et al.* [27] showed that a single nebulisation of tobramycin in healthy subjects led to high lung parenchymal concentrations with low serum levels. The same authors performed a double-blind RCT evaluating tobramycin nebulisation in patients with VAP [28]. Among the 38 patients included in that study, 21 received tobramycin and 17 received a placebo. The conclusion of that preliminary study was that tobramycin was well tolerated. However, because all patients received *i.v.* tobramycin, no conclusion on efficacy could be drawn and no pharmacokinetics data could be obtained [28].

Most data on the use of nebulised aminoglycosides have been derived from retrospective studies, thus limiting their interpretation. In a retrospective analysis, Czosnowski *et al.* [29] evaluated 49 patients who received aerosolised antibiotics for the treatment of a total of 60 episodes of VAP caused by *Pseudomonas aeruginosa* and/or *Acinetobacter baumannii*. The authors used nebulised tobramycin, amikacin and colistimethate in 44, nine and nine episodes, respectively. Systemic antibiotics were used in all except one patient. The main outcome measure was clinical success, which was achieved in 36 (73%) out of the 49 first episodes of VAP, eight (73%) out of 11 subsequent episodes, 17 (85%) out of 20 episodes that were failing *i.v.* monotherapy and 30 (79%) out of 38 episodes with MDR

 https://doi.org/10.1183/2312508X.10004716

P. aeruginosa or *A. baumannii*. Microbiological success was achieved in 29 (71%) out of 41 evaluable episodes [29].

In 2008, PALMER *et al.* [30] randomised 43 patients with purulent tracheobronchitis and Gram-stain-identified pathogens to receive aerosolised antibiotics (n=19) or placebo (n=24) through a breath-synchronised jet nebuliser. The antibiotic choice was based on tracheal aspirate Gram-staining results: patients received nebulised vancomycin if the Gram stain showed Gram-positive microorganisms and nebulised gentamicin if the Gram stain showed Gram-negative microorganisms. Most of their patients had clinical signs of VAP at the time of randomisation and were receiving systemic antibiotics. They showed that antibiotic nebulisation led to faster resolution of clinical signs of pneumonia compared with placebo, and that patients who received nebulised antibiotics had fewer subsequent VAP episodes, lower bacterial resistance and lower use of systemic antibiotics. There was a trend towards more rapid weaning from mechanical ventilation in patients who received nebulised antibiotics [30].

A few studies evaluated vibrating-mesh nebulisers in patients with VAP. Two pharmacokinetics studies evaluated amikacin penetration into the alveolar epithelial lining fluid using a breath-synchronised vibrating-mesh nebuliser not currently marketed (Pulmonary Drug Delivery System (PDDS) Clinical; Nektar Therapeutics, San Carlo, CA, USA) [31]. The authors found high amikacin concentrations in epithelial lining fluid from areas involved in infection, while the serum amikacin concentration remained low, below the toxicity level, in patients with or without acute renal failure [31, 32]. Using the same breath-synchronised vibrating-mesh nebuliser, NIEDERMAN *et al.* [33] randomised 69 mechanically ventilated patients with Gram-negative VAP to receive, as adjunct therapy to *i.v.* antimicrobials, 7–14 days of aerosolised amikacin 400 mg twice daily (n=21), amikacin 400 mg once daily and placebo 12 h later (n=26) or placebo twice daily (n=22). Aerosolised amikacin was well tolerated, without any severe adverse event, and patients who received amikacin twice daily required significantly less antibiotics than patients receiving nebulised placebo (mean number of systemic antibiotics per patient per day at the end of treatment 0.9 *versus* 1.9, respectively; p=0.02) [33]. However, the data were obtained in a relatively small number of patients and require confirmation on a larger scale.

A recent study evaluating nebulised amikacin and fosfomycin as adjunct treatment to *i.v.* antibiotics in patients with VAP using the eFlow vibrating-mesh nebuliser (PARI, Starnberg, Germany) have been completed and the results were negative: nebulisation of amikacin plus fosfomycin was not associated with improved outcome [34].

Colistin nebulisation

Nebulised colistin has been evaluated, with encouraging results, in patients with pneumonia due to MDR Gram-negative bacilli [35]. However, all studies were retrospective observational studies. The most important studies reporting on patients treated with nebulised colistin are shown in table 1. Most patients were treated with a combination of *i.v.* antibiotics in addition to nebulised colistin. In the most recent study, LU *et al.* [36] compared 122 patients with *P. aeruginosa* VAP due to a sensitive strain treated with *i.v.* antibiotics with 43 patients with *P. aeruginosa* VAP due to an MDR strain who received nebulised colistin either alone (n=28 (65%)) or in combination with 3-day *i.v.* aminoglycosides therapy (n=15 (35%)) [36]. VAP cure, VAP recurrence and mortality rates

Table 1. Main studies evaluating nebulised colistin for the treatment of VAP

First author [ref.]	Study design	Patients n	Control group	Pathogens	Pathogen eradication %	Clinical cure %	Time of evaluation	Mortality rate %
Lu [36]	Prospective cohort	43	122 patients with susceptible strains	*P. aeruginosa*, *A. baumannii*	69	67	14 days	16
Michalopoulos [37]	Prospective cohort	80	None	*P. aeruginosa*, *A. baumannii*, *K. pneumoniae*	83	83	End of antimicrobial treatment	25
Lin [38]	Retrospective cohort	45	None	*A. baumannii*	38	58	NR	42
Kwa [39]	Retrospective cohort	21	None	*P. aeruginosa*, *A. baumannii*	86	57	NR	47
Berlana [40]	Retrospective cohort	70	None	*P. aeruginosa*, *A. baumannii*	92	NR	NR	18

P. aeruginosa: *Pseudomonas aeruginosa*; *A. baumannii*: *Acinetobacter baumannii*; *K. pneumoniae*: *Klebsiella pneumoniae*; NR: not reported.

https://doi.org/10.1183/2312508X.10004716

were similar in patients infected with sensitive-strain *P. aeruginosa* and in patients infected with MDR strains [36].

Interestingly, none of these studies reported the emergence of colistin-resistant pathogens or renal toxicity due to colistin nebulisation [35–41].

A randomised placebo-controlled double-blind study evaluated patients with Gram-negative VAP who received either nebulised colistin (n=51) or nebulised placebo (n=49) in addition to *i.v.* antibiotics [42]. Clinical outcomes (clinical cure, mortality and VAP-attributed mortality) were similar in the two groups, whereas the microbiological cure rate was higher in patients receiving nebulised colistin than those receiving placebo. Complications were similar between groups [42].

Other antibiotics

Zarrilli *et al.* [43] recently showed that for patients on mechanical ventilation receiving vancomycin for MRSA pneumonia, vancomycin concentrations in their tracheal aspirates were very low and sometimes below the therapeutic range. When patients were given aerosolised vancomycin as adjunct therapy to *i.v.* vancomycin, tracheal aspirate antibiotic concentrations rose and they were always above the therapeutic range. However, the data were obtained in a small number of patients and need to be confirmed in larger trials.

One RCT aimed to compare two different antimicrobial treatment modalities for patients with *Pseudomonas aeruginosa* VAP: one based on *i.v.* antibiotics and one in which patients would be treated only by aerosolised antibiotics [44]. In total, 40 patients were randomised to receive *i.v.* or aerosolised antibiotics: in the *i.v.* group, 17 patients received ceftazidime and amikacin, and three received ceftazidime and ciprofloxacin; in the aerosol group, 20 patients received ceftazidime and amikacin. Rates of successful treatment (defined as clinical cure), treatment failure and superinfection were similar for the aerosol and *i.v.* groups (70% *versus* 55%, 15% *versus* 30% and 15% *versus* 30%, respectively). However, the study had several limitations: it was not blinded, most patients in both arms had received *i.v.* empiric antibiotics and patients that had received antibiotics active against *P. aeruginosa* for >24 h were excluded. It should also be noted that in patients allocated to the aerosol arm antibiotics were aerosolised over a total of 8–9 h·day^{-1}, requiring deep sedation that might have led to mechanical ventilation prolongation. Indeed, although not significant, the median duration of mechanical ventilation after randomisation in the aerosol arm was longer than in the *i.v.* arm (14 *versus* 8 days) [44].

Meta-analyses and systematic reviews

Three meta-analyses were performed recently, with mixed results [26, 45, 46]. Valachis *et al.* [46] evaluated the efficacy and safety of aerosolised colistin as adjunct therapy to *i.v.* antimicrobials or as monotherapy in the treatment of VAP: 16 studies were included in their meta-analysis for a total of 690 patients. A significant improvement in clinical response (odds ratio (OR) 1.57; p=0.006), microbiological eradication (OR 1.61; p=0.01) and infection-related mortality (OR 0.58; p=0.04) was observed with the addition of aerosolised colistin to *i.v.* treatment, whereas overall mortality (OR 0.74; p=0.06) and nephrotoxicity (OR 1.18; p=0.45) were not affected. Relatively similar results were found by Liu *et al.* [45] in an analysis of nine studies that compared a combination of *i.v.* plus

nebulised polymyxin *versus i.v.* polymyxin alone in a total of 672 patients: the combination of *i.v.* plus nebulised colistin was associated with higher rates of clinical cure or improvement and pathogen eradication, and lower all-cause mortality. However, in the meta-analysis by Zampieri *et al.* [26] that included six RCTs for a total of 812 patients, nebulised antibiotics were not associated with microbiological cure (risk ratio 1.24, 95% CI 0.95–1.62), mortality (risk ratio 0.90, 95% CI 0.76–1.08), duration of mechanical ventilation (standardised mean difference −0.10 days, 95% CI −1.22–1.00), ICU length of stay (standardised mean difference 0.14 days, 95% CI −0.46–0.73) or renal toxicity (risk ratio 1.05, 95% CI 0.70–1.57).

How best to deliver antibiotics to the lung?

The main limitation of nebulisation is that a part of the nebulised drug is trapped in the ventilator circuit and the upper airways by impaction [13]. This impaction of aerosol droplets is driven by the size of particles, but also by the turbulence generated in the gas flow. Indeed, several factors can influence nebulisation efficiency: the generator, the size of the particles (which depend on the generator itself), the ventilator settings and circuit, the drug (dose and formulation) and the individual patient. Although the latter is a fixed factor, the others can be modified to increase nebulisation efficiency [47].

Aerosol generator

There are three types of nebulisers, each with different specificities and drawbacks: jet, ultrasonic and vibrating-mesh/plate nebulisers [4, 8, 16]. The potential advantages and drawbacks of the three types of nebulisers are listed in table 2.

Jet nebulisers use air or oxygen under high pressure to generate the aerosol; the gas coming either from a wall system (the generated flow is continuous, during the inspiratory and expiratory phases) or from the ventilator (the flow is intermittent, during the inspiratory phase: the device is connected to the ventilator and the driving pressure is provided by the ventilator itself). With this kind of nebuliser, drug delivery into the lungs might be highly variable from one generator to another, depending on the brand, the pressure of the driving gas and the position of the device on the ventilatory circuit [48]. This variability is

Table 2. Comparison of jet, ultrasonic and vibrating-mesh nebulisers

	Advantages	Drawbacks
Jet nebuliser	Small size of particles; low cost; unique use; can be breath-synchronised	Long duration of nebulisation; lower efficiency; high performance variability; high residual volume of drug
Ultrasonic nebuliser	High efficiency; high speed of drug delivery; easy to use	High cost; increase in solution temperature; hygiene concern; no breath synchronisation
Vibrating-mesh nebuliser	Very high efficiency; easy to use; low residual volume of drug	Cost; no breath synchronisation; low efficacy with viscous solutions; lack of studies in humans

 https://doi.org/10.1183/2312508X.10004716

decreased with the newer generation of ventilators, marketed with built-in nebulisers that have been tested to generate efficient aerosols during intermittent operation [4]. The efficiency of jet nebulisers is increased when the connection with the inspiratory limb is at a distance from the endotracheal tube, compared with its connection between the Y-piece and the endotracheal tube [4, 49–51].

Ultrasonic nebulisers use the vibration of a piezoelectric crystal to produce the aerosol. The aerosol particle size is inversely proportional to the piezoelectric crystal vibration frequency and drug output is directly proportional to the amplitude of crystal vibration [52]. The main advantages of this technique are the short time of nebulisation and the high flow of nebulisation [3, 53]. The size of the particles generated is larger with ultrasonic nebulisers than with jet nebulisers. This drawback can be overcome with an increase of the gas flow [48]. One of the consequences of the use of such devices is the increase in temperature of the solution by 10–15°C after a few minutes of ultrasonic nebulisation [4, 54]. Moreover, the drug solution becomes more concentrated during operation. Whether or not the increase in temperature and concentration of the drug can lead to antibiotic inactivation remains to be determined for each molecule used. Although they are more efficient than jet nebulisers [51, 53], ultrasonic nebulisers are not popular and not widely used, mostly because of their cost and the problems already mentioned.

Vibrating-mesh nebulisers are a newer generation of nebulisers. The nebuliser/reservoir unit comprises the aerosol generator and a drug reservoir. The aerosol generator consists of a high-frequency vibrating element that creates a rapid pumping of liquid droplets through tapered holes, thereby producing the aerosol. The size of the droplets depends directly on the diameter of the tapered holes and can vary from 1 to 5 μm. The nebuliser/reservoir unit is connected to the ventilator circuit through a T-piece adapter placed on the inspiratory limb of the circuit. Unlike ultrasonic nebulisers, the temperature of the solution does not change during operation of vibrating-mesh nebulisers and drugs can be nebulised with minimal risk of denaturation. Vibrating-mesh nebulisers have many advantages over jet nebulisers (table 2) [3].

A breath-synchronised version of the Aeroneb Pro (Aerogen, San Mateo, CA, USA), *i.e.* the PDDS Clinical, is currently under clinical investigation [31–33]. In this device, an air pressure feedback unit (for breath synchronisation) is connected to the inspiratory limb of the ventilator circuit and to the control module by pressure tubing. The nebuliser/reservoir operates in phasic, breath-synchronised mode only, providing aerosol during the first 75% of inspiration during mechanical ventilation [31]. Another brand of vibrating-mesh nebuliser, *i.e.* the eFlow (PARI), is also under current investigation. This device is an inline system, breath-enhanced, positioned on the inspiratory limb of the circuit [55]. A recent study in mechanically ventilated patients with VAP and ventilator-associated tracheobronchitis showed good results with high tracheal concentrations of amikacin and fosfomycin [56].

Despite very promising indications, the use of these nebulisers is limited by their high cost.

Size of the particles

During mechanical ventilation, part of the aerosol is trapped in the ventilator circuit and the endotracheal tube [50]. Large droplets (>3 μm) are more likely to impact the circuit,

whereas smaller particles (<0.5 µm) diffuse and are more likely to be expelled during expiration [50, 57, 58]. Consequently, to have a good alveolar deposition, the size of the generated particles should be at best between 1 and 3 µm. The size of the particles depends on the aerosol generator and its settings. For jet nebulisers, droplet size decreases when gas flow increases, whereas droplet size increases with increase in the ratio of liquid to gas flow. For ultrasonic nebulisers, aerosol particle size is inversely proportional to the piezoelectric crystal vibration frequency and drug output is directly proportional to the amplitude of crystal vibration. For vibrating-mesh nebulisers, droplet size is homogeneous [3, 48, 52, 57, 58].

Ventilator settings

Ventilator settings are of importance for improving lung deposition. Indeed, any turbulence in inspiratory flow may cause an increase in impaction and deposition of droplets that leads to decreased lung drug deposition. Air turbulence can be decreased by optimising ventilator settings: the best ventilator mode is volume-controlled mode (compared with pressure-controlled) with a constant inspiratory flow [59]. The tidal volume is also important as a high tidal volume is associated with a better lung deposition. Experts recommend a tidal volume of 8 $mL \cdot kg^{-1}$ [16, 60], with a long inspiratory time (which can be obtained by increasing the inspiratory/expiratory ratio) [22, 61, 62]. An inspiratory flow set at 40 $L \cdot min^{-1}$ achieved better lung deposition than an inspiratory flow set at 80 $L \cdot min^{-1}$ [4, 16, 61, 63]. To minimise loss of aerosol during expiration, it is recommended to synchronise the nebuliser on the inspiratory flow [48]. However, currently available ultrasonic and vibrating-mesh nebulisers are not breath-synchronised, and only some jet nebulisers are breath-synchronised.

Ventilator circuit

Aerosol impaction on the respiratory circuit and the tracheal tube is a limitation of nebulisation. Impaction (and thus aerosol lung deposition) is modified by the position of the nebuliser. There is no consensus on where to place the nebuliser (between the Y-piece and the endotracheal tube or on the inspiratory limb of the circuit) and with or without humidification. In earlier studies using jet nebulisers, the best place was 10–15 cm from the Y-piece on the inspiratory limb of the ventilator circuit (figure 1) [49–51]. Use of an inhalation chamber can also increase nebulisation efficiency [64]. However, a more recent experimental study showed that jet nebulisers provided the highest efficiency when placed proximal to the ventilator [65]. As previously described in other studies, heated humidity decreases the amount of delivered drug [2, 47, 65]. When using a heat/moisture exchanger, this later has to be repositioned at the end of the expiratory circuit during nebulisation (to avoid contamination of the environment by the product) and replaced at the end of the session (to avoid obstruction of the filter and thus of the expiratory circuit) [2, 48]. When using a heated humidifier, it should be switched off during nebulisation or the amount of drug should be increased [2, 48].

For ultrasonic nebulisers, it has been shown that distal or proximal placement on the ventilator circuit has no impact on its efficiency [51]. However, in an experimental study on a dual-chamber test lung using an ultrasonic nebuliser, the authors compared the deposition of albuterol according to its position [65]. They found that the highest lung deposition was obtained when the nebuliser was placed 15 cm from the Y-piece in the

 https://doi.org/10.1183/2312508X.10004716

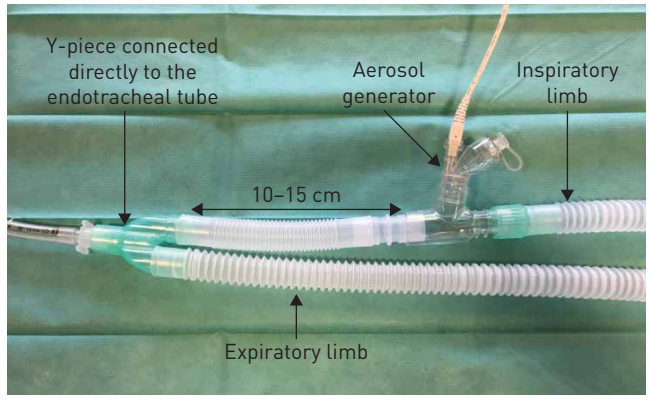

Figure 1. Position of the vibrating-mesh nebuliser on the ventilator circuit. At best, vibrating-mesh nebulisers have to be placed on the inspiratory limb of the ventilator, 10–15 cm from the Y-piece. To decrease impaction, the Y-piece should have no acute or right angles and should be connected directly to the endotracheal tube. A filter (not shown) should be placed on the expiratory limb of the circuit to avoid antibiotic nebulisation in the environment. This filter has to be replaced after each nebulisation.

inspiratory limb. Other positions of the nebuliser on the circuit (between the Y-piece and the endotracheal tube, and on the inspiratory limb of the circuit at 15 cm from the ventilator) were associated with lower efficiency. Heated/humidified and nonhumidified conditions were not found to change the deposition of albuterol [65].

Few data are available for vibrating-mesh nebulisers. Aerogen, the manufacturer of Aeroneb Pro and Aeroneb Solo, recommend the placement of the device on the inspiratory limb of the circuit, 15–30 cm from the Y-piece. In an experimental study, Ari *et al.* [65] showed that during simulated adult mechanical ventilation, placement of a vibrating-mesh nebuliser in the inspiratory limb 15 cm from the Y-piece provided the best deposition, compared with other locations. This has been confirmed recently in another *in vitro* study [63]. The placement of breath-synchronised or breath-enhanced vibrating-mesh devices currently under development (PDDS Clinical and PARI eFlow, respectively) remains to be determined. Pre-clinical studies suggest that placement between the Y-piece and the endotracheal tube could be the best option [56, 62].

Inhaled antibiotics: in which patients?

There are theoretically three main indications of antibiotic nebulisation in patients with VAP: as adjunct therapy to *i.v.* antibiotics, instead of *i.v.* antibiotics and in patients infected with MDR/XDR strains.

Should nebulised antibiotics be used as adjunct therapy to *i.v.* antibiotics? Only two randomised placebo-controlled studies have evaluated this strategy. The first compared nebulised colistin to placebo and found no difference regarding clinical outcomes [42]. The second was a pharmacokinetic study, not powered to detect any difference in outcome [33]. Therefore, due to the lack of clear data regarding this indication, we cannot recommend the use of inhaled antibiotics as adjunct treatment. One multicenter randomised placebo-controlled double-blind study evaluating amikacin nebulisation *via* the PDDS

Clinical breath-synchronised vibrating-mesh nebuliser is currently ongoing and will probably answer that crucial question (INHALE 1 (Inhaled amikacin solution BAY41-6551 as adjunctive therapy in the treatment of Gram-negative pneumonia); ClinicalTrials.gov, trial number NCT01799993).

Should nebulised antibiotics be used instead of *i.v.* therapy? Only one randomised study has evaluated this strategy: patients with *P. aeruginosa* VAP were randomly assigned to be treated with *i.v.* or nebulised antibiotics [44]. Clinical outcomes (clinical cure, relapse and mortality) were similar in both groups, but this study raised several concerns: all patients received empiric *i.v.* antibiotics, thus the true impact of nebulised antibiotics may be questionable; the procedure of nebulisation used in this study is cumbersome and may lead to prolonged mechanical ventilation; and patients with positive blood cultures (10% of VAP patients [66]) may not be eligible for such a strategy. Therefore, we cannot recommend the use of nebulised antibiotics without *i.v.* treatment for the treatment of VAP.

Should nebulised antibiotics be used in patients infected with MDR/XDR strains? This strategy has only been evaluated in retrospective studies, with apparently good results. This was confirmed by the three recently published meta-analyses [26, 45, 46] that showed a possible benefit of the use of nebulised colistin in patients with pneumonia caused by XDR pathogens. Due to the systemic toxicity of still-active antibiotics on these strains (*i.e.* colistin and aminoglycosides), nebulisation seems to be the best way to administer these drugs; it allows high drug concentrations with low toxicity. To date, this is the only indication of nebulised antibiotics that can be recommended. However, this strategy also raised a number of concerns: patients with positive blood culture or septic shock should also receive *i.v.* antibiotics and the lung delivery in patients with acute respiratory distress syndrome ventilated with low tidal volume is not known.

As already mentioned, the use of adjunct inhaled antibiotics is still in the evaluation phase. According to systematic reviews and meta-analyses results, administration of nebulised antibiotics might increase the likelihood of clinical resolution (particularly in VAP caused by resistant pathogens), but this is not translated consistently into a significant improvement of important outcomes such as mortality or duration of mechanical ventilation [26, 45, 46]. As such, and pending results of ongoing trials, the routine use of adjunct inhaled antibiotics cannot be recommended when an effective parenteral antibiotic is available. Patients with XDR, MDR and pan-drug-resistant pathogen-related infections might potentially have a higher benefit, as demonstrated by observational studies, and thus could justify the use of adjunct aerosolised antibiotics.

Our observations and recommendations in this chapter are largely consistent with existing guidelines, including those published by the Infectious Diseases Society of America/American Thoracic Society in 2016 [67]. This panel of experts also elected to recommend adjunct inhaled antibiotic therapy only for patients who are most likely to benefit; specifically, those who have VAP caused by bacteria that are only susceptible to the classes of antibiotics for which evidence of efficacy by the *i.v.* alone route is most limited (*i.e.* aminoglycosides or colistin) (weak recommendation, very-low-quality evidence). However, the panel also believes that it is reasonable to consider adjunct inhaled antibiotic therapy as a treatment of last resort for patients who are not responding to *i.v.* antibiotics alone, whether the infecting organism is or is not MDR [67].

 https://doi.org/10.1183/2312508X.10004716

Inhaled antibiotics: which dose?

Aminoglycosides

There are no recommended doses for aminoglycoside nebulisation. In the largest retrospective study published to date, the authors gave 300 mg tobramycin twice daily or 1000 mg amikacin twice daily [29]. Palmer *et al.* [30] administered 80 mg gentamicin every 8 h in patients with ventilator-associated tracheobronchitis. In the most recent studies that used a breath-synchronised vibrating-mesh nebuliser, 400 mg amikacin twice daily allowed high tracheal and epithelial lining fluid levels [31, 33]. Using nebulisers to administer aminoglycosides allows a reduction of the dose of aminoglycosides compared with *i.v.* doses [29, 30], but the exact amount of aminoglycosides to be nebulised remains to be determined and depends upon the device used.

Colistin

The most commonly reported dose for colistin nebulisation in the literature (formulated as colistimethate sodium) is 1 MIU twice daily [68]. However, based on experimental pharmacokinetic data, most authors recommend administering higher doses, 3-fold the dose commonly reported in the literature [25]. Moreover, Lu *et al.* [36] reported the use of up to 15 MIU daily (5 MIU three times daily) without significant adverse events [36]. This dose can therefore be used in patients with VAP due to MDR Gram-negative bacilli [16]; however, clinicians should monitor the trough level to avoid overdosing and toxicity.

Drawbacks of aerosolisation

Although antibiotic nebulisation appears attractive, it has several drawbacks and some questions have not yet been resolved.

Adverse effects of antibiotic nebulisation

In addition to the effects of the systematically absorbed antibiotic (*i.e.* renal toxicity for aminoglycosides and polymyxins), most adverse events result from the direct toxicity on airways and lung parenchyma (mucosa irritation). The most frequently described events are cough and a disagreeable taste [52], which are minor and transient. Bronchospasm is a more severe, possibly life-threatening, but less common side-effect that has been described in patients receiving nebulised antibiotics, especially when the *i.v.* formulation was used. Bronchospasm during aerosolisation requires the immediate withdrawal of the aerosol and β-agonist nebulisation [16, 31, 32, 52]. In the case of bronchospasm occurring during antibiotic nebulisation, re-introduction of the same drug by the same route should be avoided. As indicated earlier, one of the most serious complications of antibiotic nebulisation is the obstruction of the expiratory filter, which can lead to cardiac arrest and death, as reported by Lu *et al.* [44].

Parenchymal lung penetration

In healthy humans, nebulised antibiotic penetration into lung tissues is good [69]. However, in patients with alveolar consolidations, it is more uncertain. Most studies

evaluating aerosolised antibiotics in patients with VAP found high antibiotic levels in the tracheal aspirates [52, 70], but high sputum antibiotic levels do not necessarily mean high levels at the infection site, *i.e.* in the lung parenchyma. In piglets with experimental pneumonia, GOLDSTEIN *et al.* [24] found that amikacin penetration into the lung, even in poorly aerated areas, was good. In humans, LUYT and co-workers [31, 32] found that administering aerosolised amikacin to patients with Gram-negative VAP achieved very high aminoglycoside concentrations in epithelial lining fluids and VAP-affected lung zones, while maintaining safe serum drug concentrations. The epithelial lining fluid concentrations always exceeded the antibiotic's MIC for Gram-negative microorganisms usually responsible for VAP [31, 32]. The parenchymal lung penetration seems to be better with the newer generation of devices, *i.e.* vibrating-mesh nebulisers [31, 32, 69].

Emergence of resistant strains

Two studies looked for the emergence of resistant strains in proximal airways respiratory secretions among chronically ill patients who received adjunct inhaled antibiotic therapy [30, 71]. Interestingly, aerosolised antibiotics successfully eradicated existing MDR microorganisms and reduced the pressure from systemic agents for new respiratory resistance. However, prolonged microbiological surveillance of patients included in these studies was not performed, casting some doubt on the true value of such a strategy, all the more so as the ongoing use of aerosolised antibiotics at subtherapeutic levels outside the respiratory tract might lead to the selection of antibiotic-resistant organisms in the digestive tract [72]. Thus, as for all prevention and/or therapeutic strategies based on the use of antimicrobial agents, antibiotic nebulisation must be managed prudently, particularly concerning treatment duration, which should be kept as short as possible [73, 74].

Prolonged duration of aerosolisation

Another limitation of antibiotic aerosolisation is the long aerosolisation time required in some situations, which could lead to the prolongation of mechanical ventilation and ICU stay. Indeed, to be more efficient, antibiotic aerosolisation must be accompanied by specific ventilator settings (as discussed earlier). However, decreasing the inspiratory flow may increase patient discomfort. For many patients, physicians need to increase or start sedation to maintain patients perfectly "adapted" to their ventilator, which might lead to mechanical ventilation prolongation [44].

Cost

Most of the devices, especially the newer generation of vibrating-mesh nebulisers, are expensive. Moreover, in order to be nebulised, a special antibiotic formulation must be prepared that can also be costly. Lastly, most companies have developed antibiotic formulations to be administered *via* a specific device, thereby further increasing the cost of delivery by nebulisation [52].

Legal concerns

Most antibiotics have been approved for *i.v.* use, but not for direct delivery to the lungs. A special formulation for nebulisation exists in France for colistin and tobramycin, but the

 https://doi.org/10.1183/2312508X.10004716

use of other antibiotics is off-label [16, 52]. The situation is the same in most European countries and the USA, and it may have legal issues.

Conclusions

Antibiotic nebulisation is a promising adjunct therapy in patients with VAP [26]. However, to date, it can be only recommended for patients with VAP due to MDR strains or when the *i.v.* route is not available. In these cases, colistin and aminoglycosides are the drugs of choice, but clinicians should be aware that administration of aerosol to patients needs specific ventilator settings and close monitoring. Further studies are required before using nebulised antibiotics in day-to-day practice. Thus, administering aerosolised antibiotics alone to patients with VAP is premature at present.

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Disclosures: J. Chastre has received grants from Bayer/Nektar. He has also received personal fees from Arsanis, Bayer/Nektar, Cubist/Merck, Kenta/Aridis and Medimmune/AstraZeneca. C-E. Luyt has received grants from Bayer Healthcare. He has also received personal fees from Bayer Healthcare, Biomérieux and MSD. Both authors have received honoraria from Bayer Healthcare for having participated on advisory boards on nebulised amikacin, and are investigators of INHALE 2 (Inhaled amikacin solution (BAY 41-6551) as adjunct therapy in the treatment of Gram-negative pneumonia; ClinicalTrials.gov, trial number NCT00805168), a phase III study on nebulised amikacin using the PDDS Clinical device in patients with Gram-negative pneumonia, sponsored by Bayer Healthcare in collaboration with Nektar and Novartis.

 https://doi.org/10.1183/2312508X.10004716

Identifying patients with pneumonia due to MDR organisms coming from the community

Marta Di Pasquale, Stefano Aliberti, Paolo Tarsia and Francesco Blasi

Among patients with pneumonia coming from the community, it is crucial to identify possible MDR infections at initial diagnosis in order to select the most appropriate empirical treatment and avoid broad-spectrum antibiotic overuse. Healthcare-associated pneumonia (HCAP) criteria currently do not address this issue entirely or correctly. Recent clinical studies show that HCAP criteria do not accurately identify potential MDR organisms, as several additional risk factors associated with MDR infections are now recognised that were not included in the original HCAP definition. Personalised evaluation is therefore necessary in each patient, covering general MDR risk factors and specific risk factors related to MRSA or *Pseudomonas aeruginosa*. Scoring systems for the stratification of MDR risk could be useful in clinical practice, but they need to be developed based on local epidemiology and specific risk factors.

Cite as: Di Pasquale M, Aliberti S, Tarsia P, *et al.* Identifying patients with pneumonia due to MDR organisms coming from the community. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 97–110 [https://doi.org/10.1183/2312508X.10004816].

The theoretical gold standard of CAP treatment is represented by tailored coverage towards the causative pathogen [1–4]. Ideally, clinicians would select effective antibiotics according to the organism causing the disease and its sensitivity in order to successfully treat the infection, avoid unnecessary use of antimicrobials, and reduce adverse events and healthcare costs. Unfortunately, a microbiological diagnosis is usually missing in >70% of mild to moderate CAP cases [3]. A number of questions have been also raised in the literature concerning the type, utility and timing of diagnostic tests performed in both in- and outpatients with CAP [1–5]. The 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines recommend diagnostic testing for specific organisms when pathogens that would not respond to the usual empirical antibiotic regimens are suspected based on clinical or epidemiological data [1]. These and

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

other guidelines support a testing strategy based on patient characteristics and disease severity [1, 6]. In view of the described limitations, once a diagnosis of CAP has been made, clinicians can only guess the most likely causative pathogen based on local epidemiological data, as well as on a patient-centred analysis of the patient's risk factors for specific pathogens.

In recent decades, the microbiological pattern of pneumonia in patients coming from the community has changed. A number of reasons for this have been identified. First, the growing diffusion in the community of healthcare structures, such as haemodialysis clinics and nursing homes (nursing homes), increases the risk of translocation of pathogens, including MDR organisms (MDROs), outside the hospital [7, 8]. Second, excessive and inappropriate use of antibiotics in both humans and animals has selected resistant strains that may be implicated in LRTIs [9]. Lastly, the ageing of the population has led to an increase in both chronic diseases and long-term treatments with immunosuppressive agents, resulting in an increase in CAP patients who are not fully immunocompetent [10, 11]. There is therefore a need to identify specific populations of immunocompromised/immunosuppressed patients affected by pneumonia in terms of both identifying unusual pathogens, including opportunistic microorganisms, that may be responsible for the disease and determining the initial broad-spectrum antibiotic treatment required by these patients.

As a result of the overuse of antibiotics, some cases of pneumonia among patients coming from the community may be due to MDROs, including *Pseudomonas aeruginosa*, ESBL-producing *Enterobacteriaceae* and MRSA (collectively termed PES) [12, 13]. It is likely that infection rates and types of MDROs causing CAP will vary across different continents and among countries within the same continent as a result of varying patient characteristics, microbial ecology, healthcare systems and antibiotic use [14]. Studies performed in the USA, Europe (including Spain, Italy, Germany and the UK), Japan and South Korea have shown wide differences in the prevalence of MDR CAP, with the highest rate detected in North America (20–50%) and a much lower rate in Europe (1.1–7.6%) [15–33]. However, it should be noted that many of these studies were conducted in single centres or in only a few countries, with a retrospective design or even as a secondary analysis from administrative databases [15, 17, 20, 30–33]. One factor that could explain the broad range of percentages found is the denominator used in different studies and, in particular, whether they included all CAP patients regardless of the isolated pathogen or only those with a culture-positive pneumonia. Changing the denominator obviously influences the crude rate of MDR prevalence and misleading messages may be driven by these results.

Healthcare-associated pneumonia

Evidence of an increasing rate of MDR infections in the community in the early 2000s encouraged experts to come up with a new concept of "healthcare-associated infection". Friedman *et al.* [7] showed for the first time in 2002 that healthcare-associated bloodstream infections were similar to nosocomial infections in terms of patient characteristics, and the causative pathogens and their susceptibility patterns, as well as the mortality rate during follow-up. From these data and some preliminary and retrospective findings, the expert panel of the IDSA/ATS proposed a new classification for pneumonia in their 2005 guidelines, called healthcare-associated pneumonia (HCAP), with the aim of predicting MDROs in patients with pneumonia coming from the community [34]. This new

 https://doi.org/10.1183/2312508X.10004816

classification included CAP patients with at least one known risk factor for MDROs among the following: 1) antimicrobial therapy in the preceding 90 days, 2) residence in a nursing home or extended-care facility, 3) home infusion therapy, 4) chronic dialysis in the preceding 30 days, 5) home wound care or 6) a family member with an MDRO [34]. The recommendation was that these patients should be treated with broad-spectrum antibiotics including two antipseudomonal drugs with/without an anti-MRSA agent depending on whether MRSA risk factors were present. After the publication of these guidelines, a number of studies were carried out aimed at validating this new concept and several concerns were raised.

No studies were published on HCAP before these guidelines and the idea of a healthcare-associated infection was adopted from previously published experiences on patients with different diseases, such as bloodstream infections [7, 8]. The first study on MDR CAP published after the 2005 guidelines was a secondary analysis of the Cardinal Health-Atlas Research Database in the USA and included 4543 patients with pneumonia with positive cultures [15]. Notably, *Staphylococcus aureus* was the first pathogen causing CAP with a rate of MDROs higher than had been published previously. These data stimulated a number of controversies among the scientific community, driven mainly by the fact that MDRO prevalence was calculated only among patients with culture-positive pneumonia. First, it could be speculated that this specific population of CAP patients is very different from that encountered in real life where information on the causative pathogen is unavailable to the physician when deciding empirical antibiotic treatment. Subsequently, a number of prospective and well-designed studies, especially from Europe, reported a rate of MDROs in CAP of <8% [21, 24, 26, 29]. Second, highly heterogeneous risk factors were placed under the same umbrella definition of HCAP [35–55]: 1) previous hospitalisation did not differentiate patients admitted to either a general ward or the ICU where a different ecology might be present, 2) the definition of time limits for previous hospitalisation was predetermined and not based on any previously published evidence, 3) the length of previous hospital stay was not taken into account, and 4) different patients with a different performance status might be identified under the general "nursing homes" label. Third, the HCAP definition used over the past 10 years has been neither univocal nor standardised and is often very different from that published in the 2005 IDSA/ATS guidelines [56]. Fourth, some studies have included immunocompromised patients among those with HCAP, although there is a general consensus that this special population should be considered as a separate entity [17, 20, 57]. Fifth, an erroneous assumption was made concerning the relationship between the presence of MDROs and the risk of mortality in the HCAP population. These patients tend to have a poor performance status and several comorbidities that, by themselves, lead to a high risk of death in the case of an acute event such as pneumonia, regardless of the causative pathogen. Finally, the HCAP classification is not able to identify patients with pneumonia due to specific MDROs (*e.g.* MRSA *versus* MDR *P. aeruginosa versus* ESBL-positive pathogens), which deserve different broad-spectrum antibiotic treatments (*i.e.* vancomycin/linezolid *versus* anti-*Pseudomonas* drugs *versus* carbapenems, respectively) [27].

Overtreatment has always been one of the major concerns related to implementation of the HCAP classification in practice. Observational studies published in Europe have clearly informed the scientific community about different weights that HCAP risk factors might have in predicting MDR pneumonia [21, 24, 58–60]. Among these, nursing home residency and previous hospitalisation were the strongest predictors for MDROs in an Italian population of CAP patients [21]. Another study, conducted in the UK, found that the

frequency of MDROs was low in both CAP and HCAP cohorts, and that the increased mortality among HCAP patients was driven primarily by underlying patient-related factors rather than by the presence of antibiotic-resistant pathogens [24]. Finally, a more recent study, conducted in Spain, demonstrated that the empirical antibiotic therapy recommended for CAP might be appropriate in up to 90% of patients with HCAP [60].

All studies published between 1980 and 2013 on MDR CAP were meta-analysed by Chalmers *et al.* [14] in 2014 to determine how accurately the HCAP classification identified patients coming from the community with pneumonia due to potentially resistant pathogens. The results of this systematic review and meta-analysis raised serious concerns about the validity of the HCAP classification by demonstrating that it was poorly predictive of resistant pathogens across multiple international studies. The HCAP definition seemed to be neither sufficiently sensitive nor specific enough in identifying patients at risk for MDR bacteria, with an AUC consistently below the 0.75 threshold, especially in prospective and high-quality studies and among those designed in Europe [18, 21, 23, 24, 43, 44, 48]. The authors suggested that the use of the HCAP classification is therefore likely to lead to overtreatment in areas of low MDRO prevalence and potentially to undertreatment in areas of high MDRO prevalence. Therefore, there is a clear need for a better understanding of the local prevalence of MDROs and for the development of local guidelines addressing the MDRO issue where the prevalence is high.

In light of the evidence published in Europe following the 2005 definition of HCAP [14, 29, 58–60], the 2011 guidelines on the management of CAP published by the European Respiratory Society (ERS) did not support the use of the term HCAP as clinically relevant in Europe [6]. In line with this, the latest IDSA/ATS guidelines on nosocomial pneumonia and VAP management no longer identify HCAP as a separate entity [61]. The panel of experts specifically stated that coverage for MDROs among patients with pneumonia coming from the community would probably be based on validated risk factors for MDROs and not solely on whether or not the patient had previous contact with the healthcare system.

Risk factors associated with MDR pathogens

The HCAP experience has taught us that a better understanding of the risk factors for MDRO is warranted. Beyond those risk factors included in the HCAP definition, several others have been reported in the literature to be associated with MDR pneumonia, including demographic characteristics such as age and nursing home residency, comorbidities such as chronic renal failure and chronic lung diseases, previous hospitalisation, functional status, disease severity, and some laboratory findings (table 1) [16, 20, 24, 29, 30, 62, 63].

Of these, the main risk factors that are consistently reported to be associated with MDROs are prior hospitalisation and nursing home or long-term care facility residence [16, 20, 21, 24, 30, 62–64]. Prior hospitalisation is the most frequent risk factor and accounts for about half of all patients with MDROs [20, 21, 62, 63]. It is defined as recent contact with the healthcare system in which possible colonisation or infection with an MDR pathogen may have occurred, due to interventions such as receiving antibiotics, central line placement or invasive procedures. However, timing from discharge has not been recognised univocally in the literature, although most of the studies arbitrarily used the "preceding 90 days" as the cut-off point.

 https://doi.org/10.1183/2312508X.10004816

Table 1. Risk factors for infection with specific MDR organisms (MDROs)

Risk factor	MRSA	*Pseudomonas aeruginosa*	MDR Gram-negative bacilli
Age <30 or >79 years	✓		
Hospitalisation in prior 90 days	✓	✓	✓
Need for ICU admission	✓		
Septic shock		✓	
Residence in a nursing home	✓		
Antibiotic therapy in prior 90 days	✓	✓	✓
Chronic pulmonary disease		✓	
Smoking		✓	
Chronic kidney disease	✓		
Dialysis in prior 30 days	✓		
Congestive heart failure	✓		✓
Cardiovascular disease		✓	
Malignancy		✓	
Diabetes mellitus	✓		
Cerebrovascular disease	✓		✓
Altered mental status	✓	✓	✓
Alcoholism			✓
Immunosuppression	✓		
Positive history for MDRO colonisation/infection	✓		
Use of gastric acid-suppressive agents	✓	✓	✓
Current corticosteroid use		✓	
Enteral tube feeding		✓	
P_{aO_2}/F_{IO_2} ratio <200 or tachypnoea >30 cycles·min^{-1}		✓	
Hyponatraemia		✓	

P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction.

Prior antimicrobial therapy is also a risk factor for MDROs [16, 62, 63]. A prospective observational study in Spain evaluating 1597 CAP patients with an aetiological diagnosis showed an independent association between antibiotic use in the previous month and infection by PES [65]. These data have been confirmed by a recent prospective observational study evaluating a specific population of bacteraemic CAP patients [66].

Another crucial point that was not taken into account by the HCAP classification was the coexistence of different risk factors for MDROs in the same patient and the impact of this. Around one-third of patients presenting with pneumonia have at least one risk factor for MDRO, while 30–50% of patients coming from the community have no risk factors on admission [17, 22]. Some studies evaluated whether the presence of more than one risk factor was associated with a higher risk of MDR infection [29, 67]. In a study conducted by Shindo *et al.* [16], the cumulative incidence of pneumonia due to MDROs was 9% when no or one risk factor was present, 22% with two risk factors, 42% with three risk factors and >50% when the patient presented with four or more risk factors. Maruyama *et al.* [28] consistently showed that the incidence of pneumonia due to MDROs was only 2% when no or one risk factor was present on admission, increasing to 27% when two or more were present, in a cohort of 445 patients with pneumonia who were analysed prospectively. These results showed that not only the type of risk factor but also the number of factors

present at the same time in the same patient were associated with a higher risk of MDR infection. This could be a further tool to aid clinicians in deciding when to initiate MDR coverage. Among all the risk factors for MDROs, a special focus should be on residency in nursing homes and long-term care facilities, and on the classification of nursing home-acquired pneumonia (NHAP).

A focus on nursing home-acquired pneumonia

Pneumonia is the second most frequent infection in persons living in nursing homes. This population generally comprises elderly patients at risk of death with a poor functional status and several comorbidities [68, 69]. Although infections due to MDROs represent the greatest risk in nursing home patients, no clear association has been proven so far between MDROs and increased risk of death among these patients [70, 71]. Despite the higher rates of MDROs described in NHAP patients compared with CAP patients in some previous study, there are no evidence-based recommendations regarding the microbiological evaluation and empirical or individualised management of these patients [15, 17, 72].

In the last few decades, some studies have suggested that NHAP is a different clinical entity from CAP [69, 73–75]. Studies on NHAP patients showed that, when compared with CAP patients, these patients are not only older and have a poor performance status, but also commonly present with other specific risk factors for MDR pneumonia, such as chronic aspiration, being bedridden, malnourishment, the presence of indwelling devices, previous colonisation with resistant pathogens and previous healthcare contacts.

Global data on the prevalence of NHAP are missing, leading to a lack of knowledge about the worldwide impact of NHAP and, in particular, the microbiological patterns in different countries. Available data are mainly from the USA [15, 17], Europe [23, 27, 29] and Japan [73]. A global perspective on NHAP is warranted in light of the possible different characteristics that these institutions might have in different countries [25, 55, 72, 76]. Microbiological results are controversial, as MDRO rates differ depending on the setting. Studies in the USA found an association between MDROs and NHAP, while in Europe this association was not confirmed [15, 17].

Prediction rules for MDR pathogens

In order to overcome the limitations of the HCAP classification, a different approach to MDR risk factors has emerged in recent years. Scoring systems that weight individual risk factors differently for MDROs have progressively gained importance and have demonstrated a clear superiority compared with the HCAP classification (table 2).

In 2008, Shorr *et al.* [20] reported a clinical scoring system for MDRO risk in patients with pneumonia in the USA, assigning 4 points to recent hospitalisation, 3 points to nursing home residence, 2 points to haemodialysis and 1 point to ICU admission. The prevalence of MDROs increased with increasing scores, ranging from <20% among patients with <3 points to >75% in patients with >5 points. In 2012, this scoring system was also validated in a prospective cohort of 977 CAP patients, confirming that the score is a strong predictor for MDROs [32].

 https://doi.org/10.1183/2312508X.10004816

Table 2. Available scoring systems developed to predict MDR organisms in patients with pneumonia coming from the community

First author [ref.]	Country	Risk factors and points	Score
Shorr [20]	USA	Recent hospitalisation (4 points) Nursing home (3 points) Long-term haemodialysis (2 points) ICU admission (1 point)	<3 points (low risk) 3–5 points (intermediate risk) >6 points (high risk)
Aliberti [21]	Italy	Recent hospitalisation (4 points) Nursing home (3 points) Chronic renal failure (5 points) One or more of the following: home infusion therapy, home wound care, immunosuppression, antimicrobial therapy <90 days, COPD, diabetes, cerebrovascular disease (0.5 points)	<0.5 points (low risk) >3 points (high risk)
Park [30]	Korea	Tube feeding (5 points) Recent hospitalisation (3 points) Recent intravenous antibiotics (2 points) Admission from long-term care facility (1 point) Recent chemotherapy (1 point) Recent wound care (1 point) Chronic dialysis (1 point)	<3 points (low risk) >3 points (high risk)
Shindo [16]	Japan	Recent hospitalisation Immunosuppression Home infusion therapy Use of gastric acid-suppressive agents Tube feeding Non-ambulatory status	Each risk factor increases the risk 2-fold
Ma [63]	China	Bronchiectasis (14 points) Recent hospitalisation (5 points) Severe pneumonia (2 points) Others including: nursing home residence, home infusion therapy, chronic wound care, chronic dialysis and immunosuppression (0.5 points)	<2 points (low risk) 2.5–7 points (intermediate risk) >7.5 points (high risk)
Prina [65]	Spain	Age 40–65 years (1 point) Age >65 years (2 points) Male (1 point) Previous antibiotic use (2 points) Chronic respiratory disease (2 points) Chronic renal disease (3 points) Consciousness impairment (2 points) Fever (−1 point)	>5 points (high risk)

A different scoring system for MDROs in patients hospitalised with pneumonia coming from the community was derived in Europe in 2012 by Aliberti *et al.* [21]. The variables comprising the score are chronic renal failure (5 points), prior hospitalisation (4 points),

residence in a nursing home (3 points) and several other variables, including cerebrovascular disease, diabetes, COPD, immunosuppression, home wound care, prior antimicrobial therapy and home infusion therapy (0.5 points for the presence of one or more of these risk factors). As with the previous scoring system, prevalence of MDROs increased with higher scores, ranging from 8% among patients with a score of ⩽0.5 points to 38% among patients with a score of ⩾3 points. The Aliberti *et al.* [21] and Shorr *et al.* [20] scoring systems were subsequently validated in two independent European cohorts of patients hospitalised with pneumonia, and both showed a better predictive ability in identifying MDR CAP compared with the HCAP classification, with a significantly higher AUC [29].

Scores for infection by MDROs were also derived in Asian cohorts. In South Korea, the score comprised seven variables and was validated in 580 patients with culture-positive bacterial CAP [30, 62], and again showed better diagnostic accuracy for prediction of MDROs in comparison with HCAP criteria. In Japan, Shindo *et al.* [16] presented a scoring system in a prospective cohort of 1413 patients from a multicentre study. Six variables were taken into account for prediction of MDROs, and the AUC in this specific population of patients was higher than the scores derived and validated in the USA and Europe. Lastly, another clinical scoring system was developed in a cohort of elderly patients with pneumonia in China: the AUC of this score was higher than the HCAP definition (0.78 *versus* 0.62, respectively) [63].

Recently, a new scoring system was proposed to identify PES, which are the most common pathogens requiring a different treatment in CAP patients [65]. In this system, age 40–65 years and male sex each score 1 point, age >65 years, previous antibiotic use, chronic respiratory disorder and consciousness impairment each score 2 points, and chronic renal failure scores 3 points, whereas fever at emergency reduces the score by 1 point. The model had an AUC of 0.75, and the authors suggested that patients with a score of ⩾5 points had a high risk of presenting at least one of the PES pathogens. The development of scores in different countries is important, as the local epidemiology of MDROs and the rate of single risk factors differ depending on the geographical region.

A probabilistic approach to identifying MDR CAP has now clearly replaced the HCAP classification. Most of the scoring systems published worldwide have been shown to be more accurate than the HCAP definition in highlighting MDR CAP. No one score has proved to be better than any other at a global level. This is likely to be due to the different ecologies of CAP, different healthcare systems and different antibiotic use in different countries, and there is therefore a need to generate scores predicting MDR CAP at a local level. Furthermore, scores help clinicians identify patients who are not at risk for MDR pathogens, where broad-spectrum empirical antibiotic treatment is not needed. The number of patients who are medium or high risk for MDR infection remains a heterogeneous and large group, with many different types of patients and MDROs. Finally, every causative MDRO potentially requires treatment with different antibiotics. Therefore, it is necessary to identify the risk factors for a specific MDRO, with a special focus on PES.

Risk factors associated with specific MDR pathogens

Different studies have reported specific risk factors related to MRSA, *P. aeruginosa* and other potential MDROs in patients with CAP and HCAP, as summarised in table 1.

 https://doi.org/10.1183/2312508X.10004816

MRSA

MRSA is the most frequent causative pathogen among MDROs in patients with pneumonia coming from the community [21, 24, 32]. This consideration justifies the current effort in identifying specific risk factors for this pathogen in order to tailor anti-MRSA empirical treatment where required.

Multiple studies detected hospitalisation in the previous 90 days and the need for ICU admission as frequent risk factors related to MRSA among CAP patients [20, 24, 32, 72, 77]. One of these studies recognised nursing home residency as an additional risk factor associated with MRSA infection [20]. In a Japanese cohort of 1413 patients hospitalised with pneumonia, the incidence of MRSA was 9.6% in patients with all types of pneumonia [16]. In this study, factors independently associated with MRSA were chronic dialysis during the preceding 30 days, a positive MRSA history and congestive heart failure (specific for MRSA), whereas hospitalisation during the preceding 90 days, use of antibiotics within the previous 90 days and use of gastric acid-suppressive agents were risk factors both for MRSA and other MDROs. The incidence of MRSA pneumonia reached 36% when patients had at least one of the three MRSA-specific risk factors and two or more risk factors for MDROs (either MRSA or non-MRSA MDR pathogens). Among a Spanish population of hospitalised CAP patients, Prina *et al.* [65] found a 1.3% prevalence of MRSA pneumonia, with diabetes mellitus, chronic kidney disease and altered mental status at diagnosis being associated with MRSA. However, these studies had several limitations. First, they were mainly secondary analyses of large databases and single-centre studies. Second, not all of the known risk factors for MRSA were evaluated systematically across these populations and the limited samples often did not allow the performance of multivariate analysis to identify exclusive risk factors for MRSA.

In order to address this topic in a systematic way and from a global perspective, an international, point-prevalence multicentre study enrolling 3702 adult CAP patients, the GLIMP (Global initiative for MRSA pneumonia) study, was published in 2016 [78]. Investigators from 222 hospitals in 54 countries across five continents recruited all patients hospitalised with CAP on four randomly selected days in 2015. In total, 72 risk factors for MRSA and other MDROs were collected. The overall prevalence of MRSA pneumonia among all the CAP patients was 3% worldwide, with substantial differences among continents and among countries within the same continent. Three risk factors were independently associated with MRSA CAP: 1) previous MRSA infection or colonisation, 2) recurrent skin infections and 3) severe pneumonia. These results advocate an evaluation of MRSA CAP prevalence at a local level and the analysis of specific risk factors for MRSA in each patient at the time of hospitalisation before including an anti-MRSA agent among the antibiotics chosen for empirical therapy.

P. aeruginosa

The evaluation of local prevalence patterns along with specific risk factors is also warranted for other MDROs. The 2007 IDSA/ATS guidelines state that *P. aeruginosa* infection is associated with multiple risk factors in patients with pneumonia coming from the community [1]. However, a recent study on a cohort of 402 *P. aeruginosa* CAP patients found that the risk factors recommended by the IDSA/ATS guidelines (bronchiectasis, COPD with systemic steroids and/or prior antibiotic therapy) detected only one-third of

the patients with CAP due to *P. aeruginosa* [67]. Several studies have identified risk factors for *P. aeruginosa* infection in patients with pneumonia. Pulmonary comorbidities and previous hospitalisation were independently associated with *P. aeruginosa* CAP in Spain [13]. Similarly, researchers from CAPNETZ (German Competence Network for CAP) found that chronic respiratory disease and enteral tube feeding administration were independent risk factors for *P. aeruginosa* pneumonia in a cohort of more than 5000 CAP patients [79]. In a prospective cohort of 1597 CAP patients with aetiological diagnosis, Prina *et al.* [65] identified previous antibiotic use, chronic respiratory disease (defined as COPD plus bronchiectasis) and an arterial oxygen tension/inspiratory oxygen fraction (PaO_2/FIO_2) ratio of <200 as independent risk factors related to the presence of *P. aeruginosa*, whereas acute influenza symptoms and fever (>37.8°C) were protective factors. Other studies have also evaluated risk factors for *P. aeruginosa* pneumonia along with other Gram-negative bacilli [80, 81].

The identification of *P. aeruginosa* CAP is crucial to tailor correct empirical antimicrobial coverage, especially for patients at risk of infection with MDR *P. aeruginosa*. One study included *P. aeruginosa* in the group of MDR pathogens, even though it was a non-MDR strain [65]. Therefore, including all strains of *P. aeruginosa* in the MDR pathogens group may have produced some confusion regarding specific risk factors. It is essential to identify and discriminate the risk factors for *P. aeruginosa* in general from the risk factors specific for MDR *P. aeruginosa*. Endeavours similar to the GLIMP study would give invaluable results to correctly evaluate the prevalence of *P. aeruginosa* CAP worldwide and to identify specific risk factors for both susceptible and MDR strains.

Other MDR pathogens

Other potential MDROs in CAP are *Enterobacteriaceae* and *Acinetobacter* spp. Few studies have evaluated the role of these pathogens in CAP. In the CAPNETZ study, congestive heart failure and cerebrovascular disease were associated with *Enterobacteriaceae*-related pneumonia [79]. Hazardous alcohol intake was shown to be a risk factor for *Acinetobacter* in a cohort of 41 patients with pneumonia caused by *Acinetobacter* spp. in Australia [82]. Further epidemiological surveillance programmes are needed to reassess the value of ESBL-producing *Enterobacteriaceae* and *Acinetobacter* spp. as a cause of CAP.

Conclusions

Patients with pneumonia coming from the community need an individual evaluation of all possible risk factors for MDROs in order to choose the most effective empirical antibiotic treatment and avoid broad-spectrum antibiotic overuse.

It is now clear that the HCAP definition does not accurately identify potential MDROs in patients admitted with pneumonia. The 2011 ERS guidelines found no evidence in Europe to support the HCAP concept as clinically relevant [6]. Thus, the IDSA/ATS guidelines published in 2016 on nosocomial pneumonia and VAP did not include the HCAP classification, as the experts stated that empirical therapy for MDR pathogens among patients with pneumonia coming from the community should probably be based on validated risk factors for single MDROs, not solely on whether or not the patient had had previous contact with the healthcare system [61].

 https://doi.org/10.1183/2312508X.10004816

The evaluation of risk factors for MDROs starts from local epidemiological data. If the rate of MDR CAP is low, it might not be necessary to implement standard operating procedures to tackle this problem. Unfortunately, the scientific community has not yet addressed what would be the right threshold MDRO rate to consider in CAP, although a value of >5–10% might be reasonable.

In contexts where the observed rate of MDR CAP seems to be clinically relevant, it is important to exclude those patients who are not at risk for MDR bacteria so they can be treated according to local guidelines for the usual CAP pathogens. To achieve this goal and avoid overtreatment, it would be useful to develop and validate national predictive scores for MDROs based on local epidemiology and the presence of specific risk factors, thus avoiding implementing scores developed in other countries based on diverse settings.

Finally, among patients who may be at risk for MDROs, it is essential to select those at risk for a specific pathogen, foremost MRSA, but also both MDR and non-MDR *P. aeruginosa* and ESBL-producing bacteria, in order to administrate the appropriate empirical antibiotic therapy.

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Disclosures: S. Aliberti has received grants from Bayer Healthcare, Aradigm Corporation, Griffols, European Respiratory Society and Chiesi. He has also received personal fees from Bayer Healthcare, Aradigm Corporation, European Respiratory Society, Griffols, AstraZeneca, Basilea, Zambon, Novartis, Raptor, Chiesi and Actavis UK Ltd. F. Blasi has received grants from Bayer, Chiesi, Guidotti, Menarini, Pfizer, Teva and Zambon. He has also received personal fees from AstraZeneca, Bayer, Chiesi, Dompe, Guidotti, Menarini, Novartis, Pfizer, Teva and Zambon.

 https://doi.org/10.1183/2312508X.10004816

Antibiotic stewardship in the community

Eleni Papakonstantinou and Daiana Stolz

LRTIs in the outpatient setting are the most common reason for antibiotic prescription worldwide. However, the vast majority of infected patients would recover uneventfully without antimicrobial drugs. The overuse or misuse of antibiotics continues to increase at the same time that the development of novel antimicrobial agents has slowed down. Therefore, there is an urgent need to optimise antibiotic usage in order to improve patient outcomes, decrease adverse consequences (*e.g.* adverse drug reactions and antimicrobial-associated infections), reduce or prevent antimicrobial resistance and deliver cost-effective therapy. Antimicrobial stewardship has become an important strategy to fight antibiotic misuse and refers to the responsible use of antimicrobials by healthcare professionals and, moreover, to the appropriate selection of antibiotics, duration of treatment, dosage and route of administration for each patient with a suspected infection. In this chapter, we highlight the problems that arise from the overuse and/or misuse of antibiotics, and discuss the principles for antibiotic stewardship for LRTIs in the community.

Cite as: Papakonstantinou E, Stolz D. Antibiotic stewardship in the community. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 111–126 [https://doi.org/10.1183/2312508X.10004916].

Overuse and misuse of antibiotics is a growing problem in the community, resulting from insufficient awareness of the antimicrobial resistance problem by patients and primary care providers. Antibiotic stewardship programmes aim to optimise the use of antimicrobial agents and should be a focused, multidisciplinary effort of the healthcare systems in every country. In the community, such stewardship programmes aim to: 1) improve patient outcomes, 2) decrease adverse effects (*e.g.* adverse drug reactions and antimicrobial-associated infections), 3) reduce or prevent antimicrobial resistance and 4) provide cost-effective therapy.

As LRTIs are the leading cause of consultations in primary care and account for the majority of all antibiotics prescribed in clinical practice, in the first part of this chapter we describe the evidence regarding aetiology and the existing guidelines for antibiotic prescriptions in LRTIs. Auscultation, fever, discoloured sputum and breathlessness,

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

together with a general impression of the illness course, familiarity with the patient, comorbidities and age, are the main individual clinical factors that influence antibiotic prescription by primary care physicians [1]. However, some of these factors can be overemphasised and may lead to unhelpful variations in the management of LRTIs.

Rapid and accurate diagnosis, timely antimicrobial administration, and close follow-up are the cornerstones of effective management of LRTIs. Chest radiographs, CT scans and lung ultrasound are among the most popular imaging techniques that are widely used for the diagnosis of LRTIs. Molecular diagnostics, including multiplex PCR, may improve the accuracy of microbiological, including virological, diagnosis. The use of valuable diagnostic and prognostic biomarkers is also discussed, such as CRP and PCT. Finally, the effectiveness of vaccination in the prevention of bacterial and viral infections, as well as in herd protection, is described.

Antibiotic stewardship in the community should include guidelines for: 1) proper diagnosis based on risk assessment, imaging, microbiology including virology, and diagnostic biomarkers, 2) proper management, emphasising the use of antibiotics with a narrow spectrum and short duration of treatment and at an appropriate dosage, and 3) proper prophylaxis by vaccination. These guidelines should be reviewed regularly and will contribute to the identification of appropriate cases for antibiotic treatment, the provision of cost-effective treatment and a reduction in infections by MDR microorganisms (figure 1).

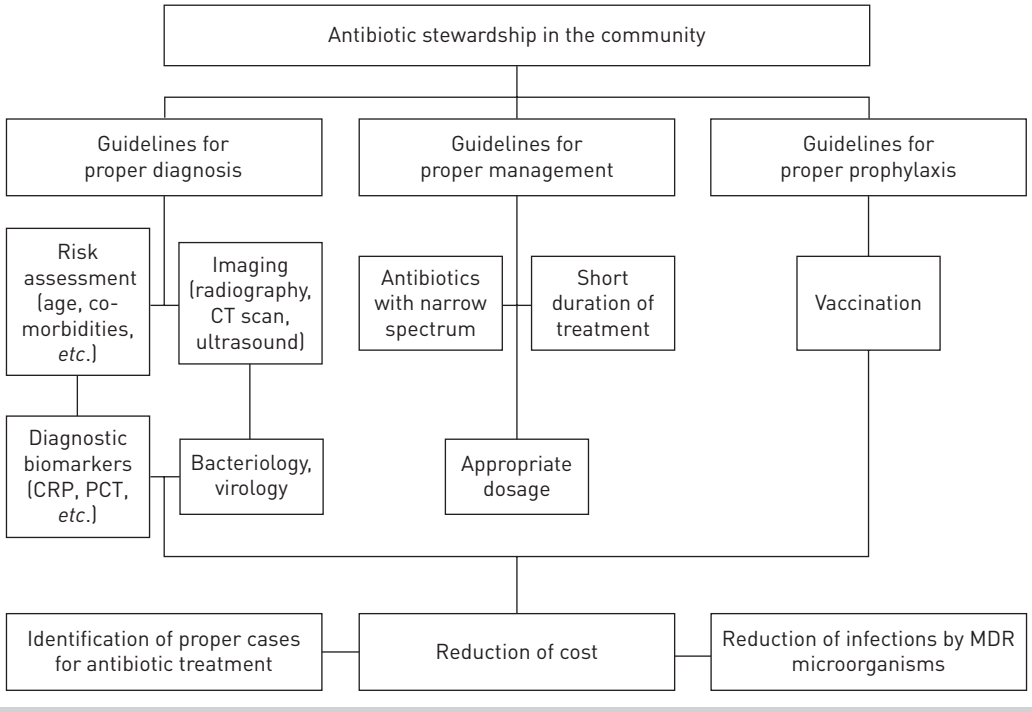
Antibiotic stewardship in the community
Guidelines for proper diagnosis
Guidelines for proper management
Guidelines for proper prophylaxis
Risk assessment (age, co-morbidities, *etc*.)
Imaging (radiography, CT scan, ultrasound)
Antibiotics with narrow spectrum
Short duration of treatment
Vaccination
Diagnostic biomarkers (CRP, PCT, *etc*.)
Bacteriology, virology
Appropriate dosage
Identification of proper cases for antibiotic treatment
Reduction of cost
Reduction of infections by MDR microorganisms

Figure 1. Antibiotic stewardship in the community.

 https://doi.org/10.1183/2312508X.10004916

LRTIs and antibiotic prescribing in the community

LRTIs are the leading cause of consultations in primary care. They include acute bronchitis, acute exacerbations of chronic bronchitis, acute exacerbations of asthma, acute exacerbations of COPD and pneumonia, and they account for the majority of all antibiotics prescribed in clinical practice [2, 3]. However, >40% of antibiotics that are prescribed for LRTIs are prescribed unnecessarily, usually for viral respiratory tract infections such as acute bronchitis or the common cold. Evidence from clinical trials suggests that most antibiotic prescriptions do not help patients get better any quicker [4–6]. In a prospective observational study of 3402 patients presenting with acute cough/LRTIs in 14 primary care research networks in 13 countries, it was found that there was no clinically significant evidence for greater effectiveness of treatment from any particular major antibiotic class used in everyday European general medical practice, including tetracyclines, amoxicillin, cephalosporins, macrolides/lincosamides and amoxicillin–clavulanic acid (co-amoxiclav) [7]. Furthermore, the authors of the study confirmed that treatment with any of these antibiotics was not associated with meaningful clinical benefit compared with no antibiotic treatment [7]. They also concluded that empirical antibiotic treatment should be used with caution for acute cough/LRTIs, and that, if clinicians do decide to prescribe antibiotics, the decision about which antibiotic to use should be based primarily on considerations such as cost, the incidence of side-effects and the impact on selection of resistant organisms.

Nevertheless, antibiotics may help to prevent adverse outcomes for some patients with LRTIs. It was shown that antibiotic prescribing on the day of LRTI diagnosis was associated with a decreased rate of respiratory infection-related hospital admission and mortality related to respiratory infection [8]. For this reason, among the large number of patients with LRTIs that do not require treatment with antibiotics, it is of utmost importance to identify the small number of patients who would benefit from antibiotics, because failure to treat these patients with serious bacterial infections can result in worse outcomes.

Unfortunately, the aetiology of acute LRTIs presenting to primary care physicians is poorly established, mainly due to inadequate clinical sampling and insufficient detection methodology for pathogens, especially for respiratory viruses [5, 9, 10]. For example, using serology for respiratory viruses and atypical bacteria, evidence of infection was found in only 16% of patients with acute bronchitis [11]. When viral cultures of nasopharyngeal washings and sputum cultures for bacteria were added, infections were detected in 29% and 40% of the patients, respectively [12, 13]. When induced sputum, urine, saliva, throat swabs and serum were included in the analysis, 44% of patients were identified as positive for pathogens [10].

Once nucleic acid amplification assays started to be used to detect both bacteria and viruses in acute adult LRTIs in primary care, using throat swabs, nasal aspirates and sputum, it was found that the majority of mild LRTIs had a viral aetiology; however, mixed viral/bacterial infections were also common and patients with a bacterial aetiology could not be distinguished clinically from patients with viral LRTIs [14]. Viruses were detected in 63% of patients; the most common viruses were rhinoviruses in 33% of patients, influenza viruses in 24% of patients and coronaviruses in 6% of patients [14]. The same viruses were also detected in another study that used throat swabs alone: bacterial infections were detected in 26% of patients, with *Streptococcus pneumoniae* being the most prominent infection in 19% of patients [9].

Risks associated with antibiotics overuse and misuse

The overuse as well as the misuse of antibiotics is associated with numerous adverse consequences, including antimicrobial resistance, the rate of which has exploded at the same time as pharmaceutical companies reduce their research and the development of new agents that could be useful to combat the emergence of resistance [15–18]. Some investigators have described the situation as a "storm" for healthcare systems, highlighting the importance of antibiotic stewardship [19].

It has been demonstrated for various bacteria and types of infection that antimicrobial resistance is associated with increased patient mortality and longer hospitalisation [20, 21]. Healthcare costs are also dramatically higher for patients infected with antimicrobial-resistant bacteria [21]. Additionally, patients who are prescribed antibiotics unnecessarily are put at risk for adverse drug reactions, such as allergic reactions, or infection with *Clostridium difficile*.

Guidelines for antibiotic prescriptions for LRTIs

According to guidelines, antibiotic treatment should be considered in patients with LRTIs in the following situations [22, 23]: 1) in cases of suspected or definite pneumonia; a patient should be suspected of having pneumonia when acute cough is present, together with one of the following signs/symptoms: new focal chest signs, dyspnoea, tachypnoea or fever lasting >4 days; in the case of pneumonia suspicion, a chest radiograph is recommended to confirm the diagnosis; and 2) for patients with LRTIs and serious comorbidities such as: a) selected exacerbations of COPD when patients have increased dyspnoea, increased sputum volume and increased sputum purulence; antibiotics should also be considered when patients with severe COPD are having an exacerbation; b) cardiac failure, especially when they are >65 years, with orthopnoea, a displaced apex beat and/or a history of myocardial infarction; c) insulin-dependent diabetes mellitus or d) serious neurological disorders (stroke, *etc.*).

Clinical recovery should be noted within 3 days of treatment with antibiotics, otherwise the patient should be re-evaluated for the presence of a different diagnosis or complications of the infection.

The American College of Physicians and the Centers for Disease Control and Prevention performed a narrative literature review of evidence about appropriate antibiotic use for acute respiratory tract infections and concluded that: 1) clinicians should not initiate antibiotic therapy in patients with bronchitis if pneumonia is not suspected, 2) patients with symptoms suggesting group A streptococcal pharyngitis should be tested by a rapid antigen detection test and/or culture, and if confirmed with streptococcal pharyngitis should be treated with antibiotics, 3) clinicians should not prescribe antibiotics for patients with a common cold, and 4) treatment with antibiotics should be reserved for acute rhinosinusitis for patients with persistent symptoms for >10 days, onset of severe symptoms or signs of high fever (>39°C) and purulent nasal discharge or facial pain lasting for ⩾3 consecutive days, or onset of worsening symptoms following a typical viral illness that lasted 5 days and was initially improving ("double sickening") [24].

 https://doi.org/10.1183/2312508X.10004916

There is insufficient evidence regarding the choice of antibiotics based on expert consensus, as also revealed by a recent systematic review for the treatment of CAP, which concluded that there is inadequate evidence to recommend one antibiotic class over another [25]. Therefore, there is wide variation among European countries in the choice of antibiotics for patients with LRTIs in primary care. Guidelines for the management of LRTIs in adults from the European Respiratory Society and the European Society of Clinical Microbiology and Infectious Diseases recommend amoxicillin or tetracycline as a first-line agent for patients who need to start antibiotic therapy [22]. The benefits and harm from high doses of amoxicillin (1 g three times daily for 7 days) for acute LRTIs in primary care when pneumonia is not suspected have been investigated in a multicentre RCT, which comprised 1038 patients assigned to the amoxicillin group and 1023 patients to the placebo group [26]. Neither the duration of symptoms rated "moderately bad" or worse nor mean symptom severity differed significantly between the groups. New or worsening symptoms were significantly less common in the amoxicillin group than in the placebo group and cases with nausea, rash or diarrhoea were significantly more common in the amoxicillin group than in the placebo group. Therefore, amoxicillin was shown to provide little benefit for acute LRTIs in primary care, both overall and in patients aged ⩾60 years, and caused minor side-effects [26].

Most major guidelines suggest an empirical treatment stratified according to disease severity [23, 27]. General practitioners (GPs) usually prescribe early, newer broad-spectrum agents because they believe that these will give the patient the best chance of a rapid cure and will prevent hospital admissions [28]. Good alternatives in the case of hypersensitivity, in countries with low pneumococcal macrolide resistance, are the newer macrolides, such as azithromycin, roxithromycin or clarithromycin. National/local resistance rates should be considered when choosing a particular antibiotic. These are documented, in detail, in the guidelines for the management of adult LRTIs by Woodhead *et al.* [23]. In this respect, when there are clinically relevant bacterial resistance rates against all first-choice agents, treatment with levofloxacin or moxifloxacin may be considered [22].

Orally administrated cephalosporins are usually not effective due to unfavourable bioavailability and low licensed dosages [29]. Coverage of atypical bacteria is usually achieved by macrolides, fluoroquinolones or tetracyclines, and most guidelines recommend oral penicillins or aminopenicillins, which have a longer half-life, higher bioavailability and better effectiveness against *Haemophilus influenzae*, to cover pneumococci [23, 27]. Differences in regional bacterial resistance rates sometimes justify the use of agents such as fluoroquinolones for acute cough/LRTIs (*e.g.* as described by GRACE (Genomics to Combat Resistance Against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) and Wood *et al.* [28]).

In addition to covering "atypical" pathogens, macrolides are also prescribed for their anti-inflammatory properties, as they decrease the expression of pro-inflammatory cytokines and consecutive recruitment of neutrophils to the lung parenchyma [30]. However, due to cardiotoxicity, the use of macrolides has been linked to slightly increased mortality. Of all the macrolides, erythromycin is associated with the greatest risk of QT prolongation and torsades de pointes, followed by clarithromycin and azithromycin [31]. Nevertheless, despite evidence for the increased risk of cardiovascular events [32, 33], the benefit of azithromycin in reducing CAP mortality outweighs the risk of cardiotoxicity [34].

There is wide variation in antibiotic prescribing for ambulatory patients in Europe [35]. The proportion of European patients consulting in general practice with LRTIs who are

prescribed antibiotics ranges from about 27% in the Netherlands (for cough and bronchitis) to 75% in the UK [36, 37]. The variation in antibiotic prescribing for acute cough was investigated in a cross-sectional observational study with clinicians from 14 primary care research networks in 13 European countries [38]. Amoxicillin accounted for 29% of prescriptions, ranging from 3% in Tromsø (Norway) to 83% in the Southampton (UK) network. Macrolides/lincosamides were prescribed for 26% of patients, ranging from 4% in Utrecht (the Netherlands) to 50%, 45% and 38% in the Bratislava (Slovakia), Milan (Italy) and Lodz (Poland) networks, respectively. Co-amoxiclav was prescribed for 15% of patients, although this varied widely, from 0% in Jönköping (Sweden) and Tromsø to 47% in Barcelona (Spain). Tetracyclines were prescribed for 14% of patients. Three networks did not prescribe tetracyclines at all (Barcelona, Mataro (Spain) and Milan), while they were the first choice in three networks (Utrecht 72%, Jönköping 56% and Helsinki (Finland) 51%). Cephalosporins were prescribed for 7% of patients (ranging from 0% to 13%) and fluoroquinolones for 5% of patients. Fluoroquinolones were most commonly prescribed in the Milan, Mataro and Balatonfüred (Hungary) networks (18%, 16% and 13%, respectively), and were not prescribed at all in six networks (Southampton, Barcelona, Lodz, Jönköping, Tromsø and Helsinki). These significant variations among networks remained after adjustment for clinical presentation.

Factors influencing antibiotics prescription

Clinical assessment is usually what most primary care physicians use to decide on the management of patients. However, physical examination and medical history do not clearly differentiate clinical syndromes, aetiology and prognosis [39–42]. In a questionnaire study from Belgium and in a direct observational study in Germany, the authors identified factors that GPs use in diagnostic decisions regarding patients with cough [39, 43, 44].

Clinicians reported four main individual clinical factors that guided their antibiotic prescribing decision for LRTIs: auscultation, fever, discoloured sputum and breathlessness [1]. They also considered the general impression of the illness course, familiarity with the patient, comorbidities and age. It was concluded that, as some of these factors may be overemphasised, given the evolving evidence base, a greater standardisation of assessment and integration of findings may be useful to reduce unhelpful variations in management [1]. This conclusion was also supported by another observational cohort study in which auscultation abnormalities (odds ratio 11.5, 95% CI 5.4–24.7) and diarrhoea (odds ratio >11) were strongly associated with antibiotic prescribing. The study involved 247 patients and antibiotics were prescribed in 79% of the patients. Assuming that antibiotics should be prescribed only for patients with pneumonia, 86% of the patients were inappropriately prescribed antibiotics; furthermore, 16% of patients with radiographic diagnosis of pneumonia were not prescribed antibiotics [45]. Therefore, physicians should be cautious and consider the extent to which auscultation should influence their decision to prescribe antibiotics for patients with LRTIs. Undoubtedly, the predictive value of individual clinical signs in reaching evidence-based prescribing decisions should be considered.

Principles of antibiotic stewardship for LRTIs

Antimicrobial stewardship has become an important strategy that aims: 1) to ensure effective, safe and cost-effective antibiotic treatment, 2) to prevent and control

 https://doi.org/10.1183/2312508X.10004916

antimicrobial resistance by using antibiotics wisely in order to maintain a long-term effectiveness for treatment and prophylaxis, and 3) to reduce the occurrence of infections by MDR microorganisms that are difficult to treat.

The following sections describe parameters that should be considered for antibiotic guidance.

Delayed prescribing of antibiotics

It has been shown that delayed antibiotic prescriptions can limit the prescriptions by 40% [46–48] and that they are as effective as immediate prescriptions in reducing complications from respiratory tract infections, as well as reducing the need for patient re-consultation [49], suggesting that a delay offers a reasonable alternative to an immediate prescription. A Cochrane review of the use of delayed antibiotic prescribing compared with immediate or no prescribing found no differences between the strategies in terms of clinical outcome, with delayed prescribing resulting in a significant reduction in antibiotic use compared with immediate prescribing [48]. However, the satisfaction of patients concerning the outcome of consultations appeared to be lower in those receiving a delayed prescription compared with those issued one immediately [46].

In a pragmatic open-label randomised clinical trial, 405 adults with uncomplicated respiratory infections were recruited and randomised in the following prescription strategies: 1) a delayed patient-led prescription strategy, 2) a delayed prescription collection strategy requiring patients to collect their prescription from the primary care centre, 3) an immediate prescription strategy or 4) a no-antibiotic strategy [50]. Delayed prescription strategies consisted of prescribing an antibiotic to take only if the symptoms worsened or if there was no improvement several days after the medical visit. It was concluded that delayed strategies were associated with slightly greater but clinically similar symptom burden and duration, and also with substantially reduced antibiotic use when compared with an immediate strategy.

Imaging

Rapid diagnosis, timely antimicrobial administration and close follow-up are the cornerstones of effective management in pneumonia [51]. Accurate chest imaging is mandatory to confirm the diagnosis and to guide treatment. Unfortunately, chest radiography has a diagnostic accuracy of only 75% when compared with CT scans [52, 53].

In a study involving 2810 patients with acute cough and 246 GPs in 16 centres located in 12 European countries, it was shown that 140 patients (5%) had radiographic pneumonia [54]. Only 41 of these patients (29%) had been diagnosed as such on clinical grounds. The clinical judgement had a negative predictive value of 96%, a sensitivity of 29% and a specificity of 99% [54]. Therefore, even if the predictive values of the clinical judgement are helpful in routine care, the majority of diagnoses of radiographic pneumonias remain undiagnosed, and there is therefore a need to further support the detection of clinically relevant pneumonia in primary care.

In this respect, the use of chest CT scans in the diagnosis and management of patients visiting the emergency department with suspected CAP was investigated in a study of 319

patients [53]. Chest radiographs revealed parenchymal infiltrate in 188 patients. CAP was initially classified as definite in 143 patients (44.8%) and probable or possible in 172 patients (53.8%), and was excluded in four patients (1.2%). CT scans revealed a parenchymal infiltrate in 40 (33%) of the patients without infiltrate on chest radiograph, and excluded CAP in 56 (29.8%) of the 188 patients with parenchymal infiltrate on radiograph. Consequently, CT scans modified the classification in 187 (58.6%) of the patients, leading to 50.8% definite CAP patients and 28.8% excluded from CAP. After the CT scan results, antibiotics were initiated in 51 (16%) patients and discontinued in 29 (9%), and hospitalisation was decided for 22 patients and discharge for 23 patients. This study indicates that early CT scan findings complementary to chest radiography markedly affect the diagnosis and clinical management in patients with suspected CAP visiting the emergency unit [53].

The routine use of CT scans is, however, limited due to the exposure to radiation, need for patient transport and costs involved [55]. The use of ultrasound in the diagnosis and management of pneumonia is a recent exciting development in clinical medicine [56]. Lung ultrasound has many advantages, as it can be done at the bedside, does not involve ionising radiation and is rapid [57]. The use of ultrasound as an alternative to traditional radiology in pneumonia has been explored. Ultrasound had a sensitivity of 90% in detecting alveolar consolidation when compared with CT scans [58]. In the past few years, lung ultrasound has been found to be consistently accurate and reliable for the diagnosis of CAP. In a study comprising 200 patients with suspected CAP in 14 centres, all patients underwent a chest radiograph and lung ultrasound [59]. If the ultrasound was positive but the radiography was negative or inconclusive, a CT scan was performed. It was shown that ultrasound was 93% sensitive and 98% specific in those patients who were diagnosed with CAP by chest radiograph or CT scan. However, a CT scan can only be performed in specific centres, and ultrasound is not always available in a GP's office; therefore, both diagnostic techniques can be difficult to be performed at the point of care.

Molecular diagnostics

Laboratory investigation of bacterial infections generally takes 2 days: 1 day to grow the bacteria, and 1 day to identify them and test their susceptibility. During these 48 h, the patients are usually treated empirically, and in the community most treatments are entirely empirical, without the guidance of laboratory bacteriology. The most complex cases, including those who fail to respond to primary empirical therapy due to resistance, are generally those who undergo laboratory investigation, resulting in an overestimation of the prevalence of resistance [60]. If rapid bacteriological investigation could be performed at the GP's office, treatments could be better tailored to individual infections, with a profound benefit for both patients and antibiotic stewardship. In addition, there would be scope to run trials of novel narrow-spectrum antibiotics, with carefully selected patients enrolled before they had received other antibiotics. Molecular diagnostics, including multiplex PCR, may improve the accuracy of microbiological diagnosis and may drive the use of narrow-spectrum agents, which are less likely to cause harmful disruption of the gut flora [61, 62].

Biomarkers

These are soluble molecules that are released into the circulation, and can be measured using accurate and reproducible methods [63]. A valuable biomarker should differentiate

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patients from healthy individuals, normalise with therapy and predict, in a reproducible way, clinical outcomes in a specific medical condition [64]. There is a clear need for diagnostic and prognostic markers in LRTIs. Diagnostic biomarkers would help to interpret clinical features that are sometimes misleading and vary according to aetiology, bacterial or viral load and virulence, the competence of the host response and comorbidities. Prognostic markers for LRTIs will help the treating physician to handle LRTIs with certainty and to choose the appropriate treatment, duration and dose with confidence. However, despite numerous studies that have been carried out or are currently ongoing to evaluate the role of various biomarkers in LRTIs, their usefulness for differential diagnosis, definition of prognosis, treatment with antibiotics and duration of treatment is still unclear.

Two biomarkers that have been described to be useful in LRTIs are CRP and PCT.

CRP

There are several observational studies indicating that CRP may help in identifying patients with pneumonia. Significantly higher CRP values were found in confirmed CAP patients compared with healthy controls and patients with suspected CAP [65]. Flanders *et al.* [66] evaluated CRP as a possible tool in the differential diagnosis of 168 adults with cough of duration <3 weeks. CRP levels correlated with the presence of pneumonia but not with its severity.

In a systematic review by van der Meer *et al.* [67], it was shown that testing for CRP is neither sufficiently sensitive to rule out nor sufficiently specific to rule in an infiltrate on chest radiograph and bacterial aetiology of LRTIs. Furthermore, there was no evidence to support CRP as a rapid test to guide antibiotic prescriptions. Therefore, CRP appears to have a limited value to predict pneumonia. However, there are no prospective intervention studies in this respect [64]. Despite the lack of robust data, CRP at the cut-off value of 50 $mg{\cdot}L^{-1}$ might indicate the need for antibiotic treatment in symptomatic cases with suspicion of CAP [67].

In another study, comprising 3106 patients presenting to primary care with acute cough, it was shown that, in patients with mild to severe clinical presentation, a clinical rule based on symptoms and signs to predict pneumonia performed best. Addition of CRP concentration at the optimal cut-off value of >30 $mg{\cdot}L^{-1}$ improved diagnostic information [68].

It has also been shown that a reduction in the prescription of antibiotics may be achieved, especially in acute bronchitis, with the implementation of a simple methodology aimed at encouraging the prudent use of antibiotics in LRTIs, including feedback and discussion of baseline antibiotic prescription, training courses in the diagnosis of treatment of LRTIs, discussion of guidelines and patient information leaflets [69]. Moreover, this reduction may be greater with the availability of CRP tests in the offices of GPs.

The benefit of CRP as a point-of-care biomarker has been evaluated in a systematic review that comprised six studies with a total of 3284 participants with acute respiratory infections from primary care settings [70]. It was shown that, with a CRP point-of-care test, a reduction in antibiotic use was likely to be achieved; however, due to differences in the designs of the included studies, it was not possible to obtain a precise effect estimate of the reduction. Furthermore, there was no evidence suggesting that time to recovery from acute respiratory tract infections and their duration were longer, or that levels of patient satisfaction or the number of re-consultations were affected when CRP was used as a

biomarker [70]. In another study, it was shown that GPs were positive about CRP point-of-care testing for LRTIs, and that they felt it empowered them to safely prescribe fewer antibiotics without disaffecting their patients [71]. Similar results were also obtained in a cross-sectional study showing that the prediction rule for low-risk patients, including a CRP value of <20 $mg{\cdot}L^{-1}$, can considerably reduce antibiotic prescriptions, with a low risk of missing a pneumonia case [72].

In an RCT, 258 patients with LRTIs and rhinosinusitis were individually randomised to CRP assistance or routine care (control) [73]. Patients in the CRP-assisted group used fewer antibiotics than the control patients, but recovery was similar across the groups, and satisfaction with care was higher in patients managed with CRP assistance. The results of this study suggest that CRP point-of-care testing to assist in prescribing decisions, including delayed prescribing, for LRTIs and rhinosinusitis may be a useful strategy to decrease antibiotic use without compromising patient recovery.

PCT

The predictive value of PCT compared with CRP, leukocyte count (white blood cells (WBCs)) and the clinical CRB-65 (confusion, respiratory rate ⩾30 $breaths{\cdot}min^{-1}$, low blood pressure (systolic value <90 mmHg or diastolic value ⩽60 mmHg) and age ⩾65 years) score was analysed in a large study by CAPNETZ (German Competence Network for CAP) [74]. PCT, CRP, WBCs and CRB-65 were determined in 1671 patients with proven CAP at admission, and patients were followed up for 28 days. The results showed that PCT levels at admission were a better predictor of CAP severity and outcome than WBC and CRP levels, with a similar prognostic accuracy as the CRB-65 score. In addition, a PCT threshold of 0.228 $ng{\cdot}mL^{-1}$ can be used to identify low-risk patients within all CRB-65 risk groups.

PCT is useful in the assessment of the severity of CAP, as shown in a study including 545 patients with suspected LRTIs, where it was shown that PCT, and to a lesser extent CRP, improved the accuracy of currently recommended approaches for the diagnosis of CAP, thereby complementing clinical signs and symptoms [75].

Although in some studies PCT does not appear to be a significant marker for CAP [76, 77], in a more recent study it was shown that highly sensitive measurements of CRP and PCT provide a better discriminatory value of these biomarkers compared with clinical signs [75]. A prospective cluster-randomised controlled single-blinded intervention trial compared the routine use of antimicrobial therapy with PCT-guided antimicrobial treatment for LRTIs [78]. In this study, 243 patients admitted with suspected LRTIs were randomly assigned standard care or PCT-guided treatment. About one-third of the included patients were suffering from pneumonia and 25% presented with acute exacerbation of COPD. Overall, the use of PCT-guided therapy was associated with a significant reduction in antibiotic use, mainly in non-CAP patients, without adversely affecting clinical course [78]. These results were also confirmed in a multicentre study, which showed that PCT-guided intervention compared with standard guidelines resulted in similar rates of adverse outcomes, with lower rates of antibiotic exposure and antibiotic-associated adverse events [79]. However, it has to be taken into account that PCT may not offer a good differential aetiological diagnosis between viral and intracellular bacterial infections such as mycoplasmas [80, 81].

Another study investigated the diagnostic value of signs, symptoms and laboratory values in LRTIs in 243 consecutive patients with suspected LRTIs admitted to a tertiary

 https://doi.org/10.1183/2312508X.10004916

care hospital [82]. Sputum, dyspnoea, crackles, fever and leukocytes (WBCs) were insensitive and nonspecific parameters for the diagnosis of bacterial LRTIs requiring antibiotic therapy. Cough was sensitive (93.8%) but not specific (5.8%). The sensitivity of infiltrates was 96.9%, of CRP >50 $mg \cdot L^{-1}$ was 93.8% and of PCT >0.1 $ng \cdot mL^{-1}$ was 93.8% [82]. It was concluded that the overall sensitivity and specificity of signs and symptoms for bacterial LRTIs requiring antibiotic therapy was poor. In order to ascertain the need for antibiotics in LRTIs, a chest radiograph with infiltrates and a determination of CRP at a cut-off value of 50 $mg \cdot L^{-1}$ or PCT at a cut-off value of 0.1 $ng \cdot mL^{-1}$ were required [82].

In a systematic review of 14 trials with 4221 participants, it was shown that the use of PCT to guide initiation and duration of antibiotic treatment in patients with acute respiratory infections was not associated with higher mortality rates or treatment failure. Antibiotic consumption was significantly reduced across different clinical settings and acute respiratory infection diagnoses [83]. Future studies should establish cost-effectiveness, considering the costs of PCT measurement and potential savings in consumption of antibiotics and other healthcare resources, as well as secondary cost savings due to the lower risk of side-effects and reduced antimicrobial resistance. Thus, PCT at the cut-off value of 0.25 $ng \cdot mL^{-1}$ (or 0.10 $ng \cdot mL^{-1}$ in those with COPD) should indicate the need for antibiotics.

Vaccination

There are several available vaccines against pneumococci and influenza virus, which are the most frequent bacterial and viral pathogens of CAP, respectively. Combined vaccination against bacteria and viruses has been proposed to prevent co-infections, which are associated with increased mortality [84]. The standard vaccine for influenza virus contains two strains of influenza A virus and one strain of influenza B virus, selected by the World Health Organization. A major problem of this vaccine is that the elderly, who are at increased risk, exhibit an inferior response to the vaccine because of immunosenescence. According to guidelines, the influenza vaccine should be given every year to persons at increased risk for complications due to influenza, including immunocompetent adults belonging to one or more of the following categories: age >65 years, institutionalised, chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, chronic renal disease, haemoglobinopathies and females who will be in the second or third trimester of pregnancy during the influenza season [85].

There is debate over vaccination against pneumococci, as meta-analyses have shown that the vaccine has an efficacy of ~75%. However, the majority of pneumococcal pneumonia is not associated with bacteraemia, and it remains controversial whether this vaccine protects against noninvasive pneumococcal pneumonia [86].

In a study that investigated the overall effects of a 13-valent pneumococcal conjugate vaccine (PCV13) in the Dutch population, it was shown that vaccination was predicted to lower the number of invasive pneumococcal disease cases per year [87]. Furthermore, herd protection would also be expected in populations with sufficient paediatric vaccination uptake. In this respect, it has been shown that there was a pneumococcal disease reduction in unvaccinated cohorts due to herd protective effects [88–94].

Antibiotic prescription in particular respiratory diseases

There is much discussion of whether exacerbations of COPD are in fact LRTIs and studies on the role of antibiotics in acute exacerbations of COPD have shown controversial results [22]. Most of these studies included both in- and outpatients, and therefore it is uncertain whether antibiotic treatment in exacerbations in all primary care patients is beneficial [95, 96].

In an RCT of 223 patients with COPD and 265 exacerbations, the administration of doxycycline in addition to systemic corticosteroids did not show superiority over placebo and corticosteroids in terms of clinical success for the primary end-point [97]. PCT guidance for exacerbations of COPD offers a sustained advantage over standard therapy in reducing antibiotic use for up to 6 months without increasing the recurrence of exacerbation. The number-needed-to-treat (NNT) to prevent one course of antibiotics is NNT=3 [98]. CRP blood levels may also be a useful biomarker in the management of exacerbations in patients with severe disease, as it has been shown that CRP levels were higher in bacterial infections than in viral infections and cases negative for any microorganism [99]. Furthermore, CRP values of >100 $mg \cdot L^{-1}$ were associated with a 4-fold increased risk of hospital admission.

Currently, there is a general impression that only selected patients benefit from antibiotics at exacerbation of COPD. Thus, antibiotics should be prescribed only in exacerbations of COPD with all three of the following symptoms: increased dyspnoea, increased sputum volume and increased sputum purulence [22]. This was also defined *post hoc* in a hallmark study by Anthonisen *et al.* [100]. The use of PCT for antibiotic guidance at acute exacerbation of COPD seems to be a valid strategy to decrease the use of antibiotics in this population.

In contrast to pneumonia and selected COPD exacerbations, antibiotics should not be prescribed in acute bronchitis or asthma exacerbations. It was shown that azithromycin is no better than a low dose of vitamin C for acute bronchitis [101]. Furthermore, in an RCT, it was shown that azithromycin did not show any clinical benefit compared with placebo in 4582 patients with asthma exacerbations [102].

Conclusions

Undoubtedly, there is a great need to develop antibiotic stewardship programmes in Europe, which will ideally be carried out by multidisciplinary institutional teams, with the aim of improving clinical outcomes through promotion of the appropriate use of antibiotics and other antimicrobial drugs both at the hospital level and in the community [103–105]. The stewardship teams should consist, among others, of infectious disease specialists, microbiologists and pharmacists who would create a list of antibiotics with specification of restricted drugs, control of antibiotic consumption, local antimicrobial resistance and guidelines for the diagnostic procedures, as well as the initial and pathogen-specific therapy of infections. The experts should regularly review and update the guidelines to ensure that antibiotic use is proportionate to infection type and severity.

Furthermore, stewardship programmes should include epidemiological surveillance of antimicrobial resistance of key pathogens at a regional and a national level. Combining effective antimicrobial stewardship and a comprehensive infection control programme will

 https://doi.org/10.1183/2312508X.10004916

improve clinical outcomes by reducing the emergence of antibiotic resistance, limiting drug-related adverse events and minimising the risk of other unintentional consequences of antibiotic use such as *C. difficile* superinfections. Societal and healthcare-related costs, which are linked with antimicrobial-resistant infections, will then be significantly reduced.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10004916

Chapter 8

Antibiotic stewardship in the hospital setting

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Antibiotic stewardship is now an international priority in order to conserve the limited pool of available antimicrobial drugs and to reduce the burden of antibiotic-associated complications. As the most common indication for antibiotic prescribing in hospitalised patients, LRTIs are a key target for stewardship interventions. In this chapter, we review the major issues around antibiotic use in hospitals, focusing on the most common indications such as CAP and exacerbations of airways disease. The key principles of antibiotic stewardship are to avoid antibiotic prescription where treatment of bacterial infection is not required, to use the narrowest spectrum required to achieve clinical and microbiological cure, and to limit the duration of treatment where possible. Surveillance data are key to monitoring and implementing stewardship interventions. Accurate data at the local level regarding levels of antimicrobial resistance, antibiotic consumption and adherence to local antibiotic guidelines are required to support stewardship interventions. Current antibiotic use for many respiratory infections is excessive and current guidelines may not appropriately emphasise stewardship principles in many countries. Simple interventions at both the healthcare provider level and individual prescriber level can limit antibiotic resistance and improve patient outcomes.

Cite as: Chalmers JD, Pletz MW. Antibiotic stewardship in the hospital setting. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 127–149 [https://doi.org/10.1183/2312508X.10017616].

Antibiotic resistance has been variously described as an impending "apocalypse", "an impending catastrophe" and "the most pressing public health issue facing the world today" [1–3]. A combination of rising rates of antimicrobial resistance, including organisms resistant to traditionally "last-resort" antibiotics such as carbapenems and polymyxins, and a historically low rate of antibiotic discovery and development has led to the recognition that our current antibiotic policies are unsustainable [4–6]. Among the key solutions to this problem, along with stimulating new antibiotic development and investing in research to combat antimicrobial resistance mechanisms, is the preservation of the existing array of antibiotics by limiting the development of resistance [7].

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As the leading indication for antibiotic prescription in hospitals, LRTIs are an important battleground for reducing unnecessary or excessive antibiotic exposure [8]. Around two-thirds of hospital inpatients at any one time will be receiving antibiotics and, for example, in one US study of six acute care hospitals, respiratory disorders accounted for 27.6% of all antibiotic prescriptions, far higher than the next highest indication (13.1% for gastrointestinal disorders) [9].

The most common acute respiratory disorders presented to hospital are CAP, acute bronchitis, acute exacerbation of COPD and exacerbations of asthma [10–12]. Exacerbations of bronchiectasis and cystic fibrosis are less frequent [13, 14]. HAP and VAP represent a smaller population of patients, but with a large burden of broad-spectrum antibiotic use [15].

Antimicrobial stewardship principles should therefore be part of the training of all respiratory physicians responsible for acute care and an integral part of all respiratory practice guidelines.

What is antimicrobial stewardship?

The accepted definition of antimicrobial stewardship is "an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness" [16]. However, stewardship relies as much on individual physician decision making as on central policy making, and at its most simplistic, stewardship can be thought of more broadly as antibiotic practices that minimise inappropriate, unnecessary or excessive antibiotic use and therefore combat resistance [16–18].

In 2015, the UK National Institute for Health and Care Excellence issued guidance for antimicrobial stewardship [16]. The guideline emphasises the importance of different stakeholders in stewardship programmes. For example, healthcare organisations have to ensure their hospitals/care centres have established stewardship programmes, and have methods for monitoring and feeding back to prescribers on their antibiotic use, and for comparing against national trends and monitoring antibiotic-associated complications [16]. The guidelines recommend that organisations should establish antimicrobial stewardship teams to direct antimicrobial stewardship efforts in the healthcare setting [16].

The methods such teams can use to improve antibiotic prescribing include implementation of antibiotic guidelines, review of prescribing with feedback to prescribers, information technology or decision support systems and education-based programmes. Restriction of certain classes of high-risk antimicrobials may also be used [16–18].

For prescribers, the responsibility is to only use antibiotics where clinically indicated, to use the shortest effective course, to use intravenous (*i.v.*) therapy only where necessary and to follow national/international guidelines [16].

Stewardship methods and approaches

Antibiotic resistance generally, and *Clostridium difficile* infection (CDI) in particular, has increased across many European countries in recent years, linked to the use of broad-spectrum antibiotics for respiratory infections. When evaluating stewardship

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interventions designed to tackle these issues, systematic reviews demonstrate that reducing overall antibiotic burden is likely to reduce the incidence of CDI and overall resistance rates [19–21]. For example, in the meta-analysis by Feazel *et al.* [19], policies restricting cephalosporin use were effective in reducing rates of CDI (pooled risk ratio 0.50, 95% CI 0.39–0.64; p<0.0001; n=14 studies) and policies restricting fluoroquinolones were equally effective (pooled risk ratio 0.45, 95% CI 0.30–0.67; p<0.0001; n=6 studies). Antimicrobial stewardship is more complex that simply designating "good" and "bad" antibiotics; it also involves interventions designed to reduce overall antibiotic burden [21]. In this regard, guideline recommendations are somewhat conflicting: on the one hand, antibiotics with a high risk for CDIs should be avoided; on the other hand, the diverse use of antibiotics is promoted [22, 23]. A Danish university hospital promoted the empiric use of piperacillin–tazobactam plus aminoglycoside instead of third- and fourth-generation cephalosporins or fluoroquinolones to counter the rise in ESBL-producing *Klebsiella pneumoniae* bacteraemia. Indeed, they achieved a significant decrease in ESBL-producing *K. pneumoniae* infections, but saw a rise in piperacillin–tazobactam-resistant *Pseudomonas aeruginosa* [24]. An interesting approach was published by Takesue *et al.* [25], who aimed to reduce the rate of MDR *P. aeruginosa* in a 900-bed hospital by periodic antimicrobial monitoring and supervision promoting the equally distributed use of five classes of antibiotics with activity against *P. aeruginosa*. Within 18 months, they were able to reduce resistance rates against all five classes. This approach is biologically plausible as diverse selective pressure prevents the emergence of resistance against a single class of antibiotics; however, more evidence is needed.

A recent systematic review evaluated whether antimicrobial stewardship interventions have any impact on patient outcomes and antimicrobial resistance [26]. From a review of 145 studies, the authors of the review concluded that adherence to evidence-based guidelines resulted in a significant reduction in mortality (relative risk 0.65, 95% CI 0.54–0.80; p<0.0001). Bedside consultations by infectious disease physicians, especially in patients with *Staphylococcus aureus* bacteraemia, also reduced mortality [26, 27]. The impact of other interventions was less clear. In particular, restrictive antibiotic interventions produced inconsistent results, with some studies reporting increased mortality and some reporting no change or a decrease in mortality. Concerns have been raised that restricted antibiotics are replaced by other antibiotics with similar rates of antimicrobial resistance generation and adverse effects [26].

We will discuss many of these strategies (table 1 and figure 1) as they apply to LRTIs in the following sections.

Unintended consequences of antibiotic use in LRTIs

The major impact of antimicrobial use is antimicrobial resistance. A constant evolutionary selection pressure is applied to the human microbiome as a result of the high rate of community antibiotic use, but this is amplified in hospitals where up to two-thirds of patients are receiving antibiotics at any given time. Antimicrobial resistance can be viewed as an inevitable consequence of antibiotic use, with the rate of antimicrobial resistance largely following the rate of antibiotic use in a near-linear fashion [23]. This is illustrated in figure 2a for azithromycin, widely used in clinical practice for CAP, where increasing azithromycin use following its release in 1992 resulted in proportionate increases in macrolide resistance in pneumococci. In this context, the long half-live of azithromycin, resulting in lengthy subinhibitory concentrations, has been seen as a major disadvantage compared with other macrolides (figure 2b) and two RCTs in healthy volunteers have

Table 1. Commonly used antimicrobial stewardship interventions and their impact and relevance to hospitalised LRTIs

Intervention	Discussion
Empirical therapy according to guidelines	Strong evidence that this results in reduced mortality across a number of respiratory infections
Blood cultures	Little evidence this results in reduced antibiotic use
De-escalation of therapy	Safe, but performed infrequently in clinical practice
Adjustment of therapy to renal function	Can be supported by pharmacists
Intravenous to oral switch	Good evidence supporting this practice and may lead to reduced length of stay
Documented antibiotic plan	Should include drug, dose, administration route and intended duration of therapy; automatic stop dates can increase adherence to antibiotic plans
Therapeutic drug monitoring	Mainly performed for specific antimicrobials (*e.g.* aminoglycosides and vancomycin) to decrease toxicity; increasing evidence for general therapeutic drug monitoring of antibiotics to avoid underdosing in critically ill patients
Discontinuation of antibiotics where infection not confirmed	Early discontinuation of antibiotics may be aided by biomarkers; evidence for decreased mortality
Local antibiotic guidelines	Should be aligned with international guidelines where possible
Restriction of antibiotics	See discussion in text; may help to reduce excess prescribing of expensive or high-risk antibiotics, but little evidence this is effective in isolation
Bedside consultations	Review by infectious disease specialists or microbiologists may be beneficial in certain contexts (*e.g.* evidence this may reduce mortality in *Staphylococcus aureus* bacteraemia)
Assessment of patient adherence	Rarely performed and less relevant to hospital care
Implementation programmes to achieve the shortest possible duration of treatment	Evidence for PCT-guided treatment duration in ICU patients and implementation of algorithms

shown that azithromycin compared with clarithromycin selected more macrolide-resistant *Streptococcus viridans* for a longer duration [29].

There are other potential adverse effects of antibiotic use. Complications of antibiotic use are probably underestimated and underreported [30, 31]. VAN DER EERDEN *et al.* [32] reported up to 60% of hospitalised patients with CAP developed adverse effects related to antibiotics, primarily gastrointestinal, *i.v.* cannulae site complications and drug allergies. In a UK cohort of patients with hospitalised respiratory infections, MURRAY *et al.* [33] reported a rate of 31%, with gastrointestinal effects and rash the most frequent adverse effects.

A listing of all the possible adverse effects of antibiotics used in LRTIs is beyond the scope of this chapter, but a few more serious adverse effects are worthy of mention. CDI has been described as an epidemic in Europe and the USA [21]. CDI is strongly linked to antibiotic

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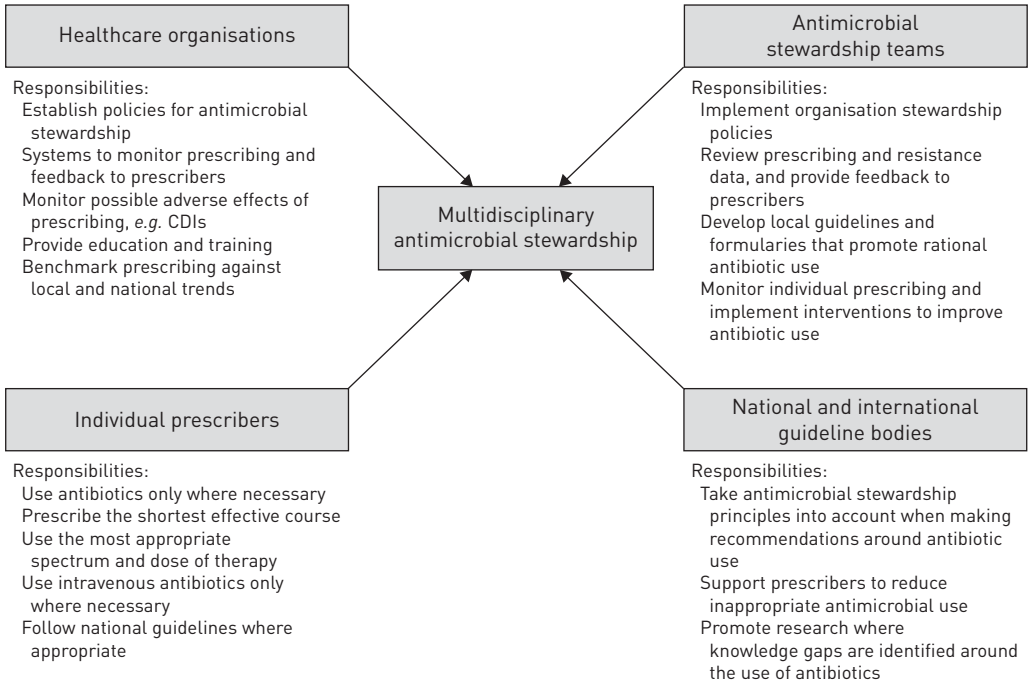
Healthcare organisations
Responsibilities:
Establish policies for antimicrobial stewardship
Systems to monitor prescribing and feedback to prescribers
Monitor possible adverse effects of prescribing, e.g. CDIs
Provide education and training
Benchmark prescribing against local and national trends
Antimicrobial stewardship teams
Responsibilities:
Implement organisation stewardship policies
Review prescribing and resistance data, and provide feedback to prescribers
Develop local guidelines and formularies that promote rational antibiotic use
Monitor individual prescribing and implement interventions to improve antibiotic use
Multidisciplinary antimicrobial stewardship
Individual prescribers
Responsibilities:
Use antibiotics only where necessary
Prescribe the shortest effective course
Use the most appropriate spectrum and dose of therapy
Use intravenous antibiotics only where necessary
Follow national guidelines where appropriate
National and international guideline bodies
Responsibilities:
Take antimicrobial stewardship principles into account when making recommendations around antibiotic use
Support prescribers to reduce inappropriate antimicrobial use
Promote research where knowledge gaps are identified around the use of antibiotics

Figure 1. Responsibilities of individual stakeholders in antimicrobial stewardship in the hospital setting. CDI: *Clostridium difficile* infection.

use in hospitals, and a direct link with respiratory infection prescribing and respiratory guidelines has previously been suggested [34]. Molecular epidemiology suggests that fluoroquinolone use has been a major driver of CDI development, along with the use of cephalosporins, amoxicillin–clavulanic acid and clindamycin [35]. Nevertheless, any antibiotic can provide the opportunity for colonisation and infection with *C. difficile* [35].

The rate of CDI in hospitals in the USA almost tripled from 5.6 to 12.7 per 1000 hospitalised patients between 2001 and 2011 [36]. UK data from 2014/2015 showed 14 000 reported cases and the recent EUCLID (European, multicentre, prospective, biannual, point-prevalence study of CDI in hospitalised patients with diarrhoea) survey showed a prevalence in European hospitals in 2011/2012 of 6.6 per 10 000 patient-bed-days increasing to 7.3 per 10 000 patient-bed-days in 2012/2013 [36–38].

The development of CDI requires the transmission of *C. difficile* and a susceptible host, usually induced by the loss of the normal gut microbiota through antibiotic use. There are now published data on the impact of CDI as a complication of CAP. Bruns *et al.* [39] studied 107 patients with CAP and found a carriage of CDI in 9.4% of patients, with a further 11.2% acquiring CDI during admission. Prolonged antibiotic duration and prior hospitalisation were the key risk factors. A large analysis from the UK published in 2016 showed that from 1883 patients with CAP, the incidence of CDI was 3.2% [40]. The risk factors for CDI were age, comorbidities, severity of CAP, duration of antibiotic therapy (9% increased risk per additional day of antibiotics), number of different antibiotics used and duration of hospitalisation. Interestingly, the implications of these two studies are that reducing antibiotic duration may reduce CDI, and that reducing total antibiotic exposure

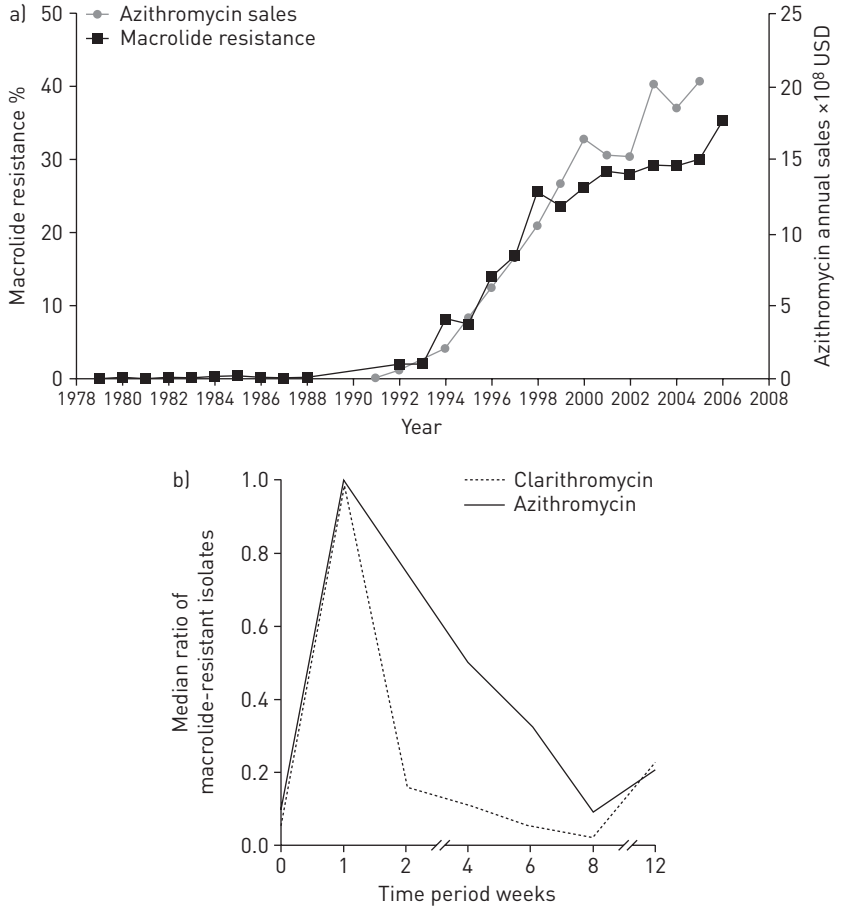

Figure 2. a) Correlation between antibiotic use and antibiotic resistance in pneumococci illustrated for azithromycin use in the USA during 1978–2008. Reproduced and modified from [28] with permission. b) Median ratio of macrolide-resistant isolates of *Streptococcus viridans* after administration of clarithromycin or azithromycin. Reproduced and modified from [29] with permission.

and removing patients as early as possible from the healthcare environment are the most effective interventions to reduce CDI [39–41]. Antibiotic class was not an independent risk factor in either study (figure 3).

There are some considerations that are specific to individual antibiotics. It is suggested that the use of fluoroquinolones for CAP therapy in areas of high TB prevalence can delay the diagnosis of TB, leading to poorer clinical outcomes [42].

Macrolides have recently been linked to a higher incidence of cardiovascular events compared with β-lactams, with prolongation of the QT interval (studies have reported an increased incidence of sudden cardiac death), destabilisation of atherosclerotic plaques (reported as a possible mechanism of ischaemic events) and the effect of large-volume *i.v.* infusions or macrolide as possible explanations for the increase in cardiovascular events [43–46]. These associations are controversial and subject to bias-by-indication as the majority of reports to date are from observational studies and the characteristics of macrolide users are typically very different from those of nonmacrolide users.

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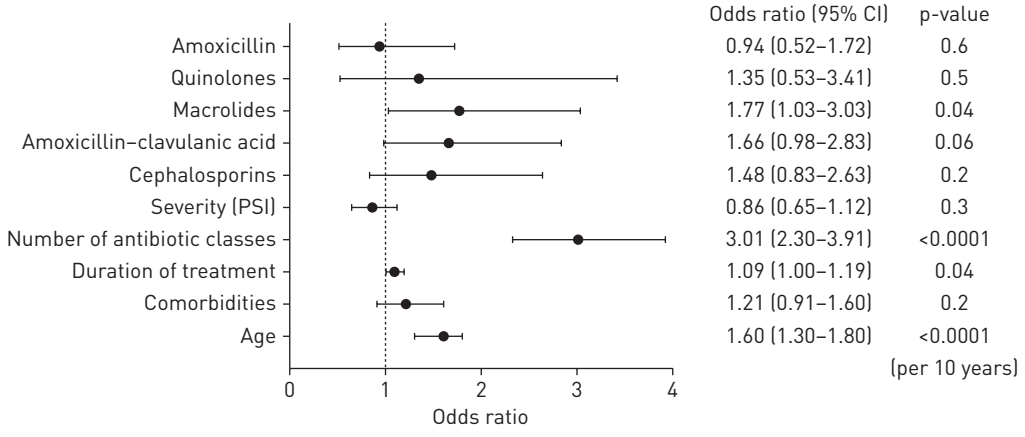

Figure 3. Risk factors for *Clostridium difficile* infection in patients hospitalised for CAP. PSI: Pneumonia Severity Index. Data from [40].

From these data it can be concluded that antibiotics used in respiratory infections carry significant side-effects and that, where possible, reducing overall antibiotic burden is desirable.

Antimicrobial stewardship in CAP

Antimicrobials in CAP are required to target the most frequent "typical" pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. aureus* and, less frequently, the *Enterobacteriaceae* [47–49]. The "atypical pathogens" *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci* and *Coxiella burnetii* account for 2–20% of CAP cases depending on the study population [49–53]. Respiratory viruses also appear to be a common and important cause of CAP, and often coexist with respiratory bacteria [52].

The worldwide epidemiology of CAP is remarkably consistent, with *S. pneumoniae* reported to be the most common pathogen across every continent. International studies also show atypical pathogens to be represented throughout the world [53–55]. In an analysis of 4337 patients, Arnold *et al.* [53] showed that atypical organisms were responsible for 22% of CAP cases in North America, 28% in Europe, 21% in Latin America, and 20% in Africa and Asia. However, there are clear differences in the prevalence of different organisms, with opportunistic organisms associated with HIV infection in sub-Saharan Africa, TB in various parts of the world, and *Burkholderia pseudomallei* in Thailand and Northern Australia being examples of specific regional differences in CAP pathogens [56–59].

Antibiotic guidelines worldwide therefore have important similarities, with the majority recommending a combination of β-lactams (penicillins, aminopenicillins, β-lactams plus β-lactamase inhibitors and cephalosporins) and antibiotics active against atypical pathogens (macrolides, fluoroquinolones and tetracyclines) [60–66]. Differences in antibiotic practice are partly based on cultural or differences in expert opinion and to some extent guided by differences in epidemiology. For example, the higher frequency of penicillin- and macrolide-resistant pneumococci in Southern Europe compared with Northern Europe results in lower usage of penicillins and higher usage of fluoroquinolones (figure 4).

A key principle of stewardship is only prescribing antibiotics to patients that require them. Accuracy of diagnosis is therefore crucial. The chest radiograph is central to this as the majority of alternative diagnoses (*e.g.* acute bronchitis, exacerbations of airways disease and cardiac failure) will also present with respiratory symptoms [71, 72]. Unfortunately, the agreement between clinicians and radiologists, or between two radiologists, is relatively low and therefore patients that are treated as CAP do not always have CAP [73, 74]. Claessens *et al.* [75] recently used chest CT to investigate this problem. They examined 319 patients with suspected CAP by chest radiography and CT. An infiltrate was found by CT in a third of patients with a "normal" chest radiograph, whereas CT excluded CAP in 30% of patients where CAP was found by radiography [75]. Thus, using CT as the gold standard test, 60% of CAP treatment decisions (positive and negative) were wrong.

Until a more reliable test is widely available we will have to continue to rely on chest radiography, but we should be aware of its limitations and consider possible alternative diagnoses, with a low threshold to discontinue antibiotics if a noninfective cause of respiratory symptoms is identified.

Once treatment is started for CAP, ongoing treatment should be rationalised to limit collateral damage. RCTs show that early *i.v.* to oral switch is achievable using clinical criteria and may be associated with a shorter length of hospital stay [76]. Indeed, the majority of studies suggest that if patients are able to swallow, the preference should be for initial therapy with oral agents [76, 77].

Antibiotic durations for CAP are excessive in many hospitals. Aliberti *et al.* [78] studied an international database of 2003 patients and demonstrated a total mean antibiotic duration

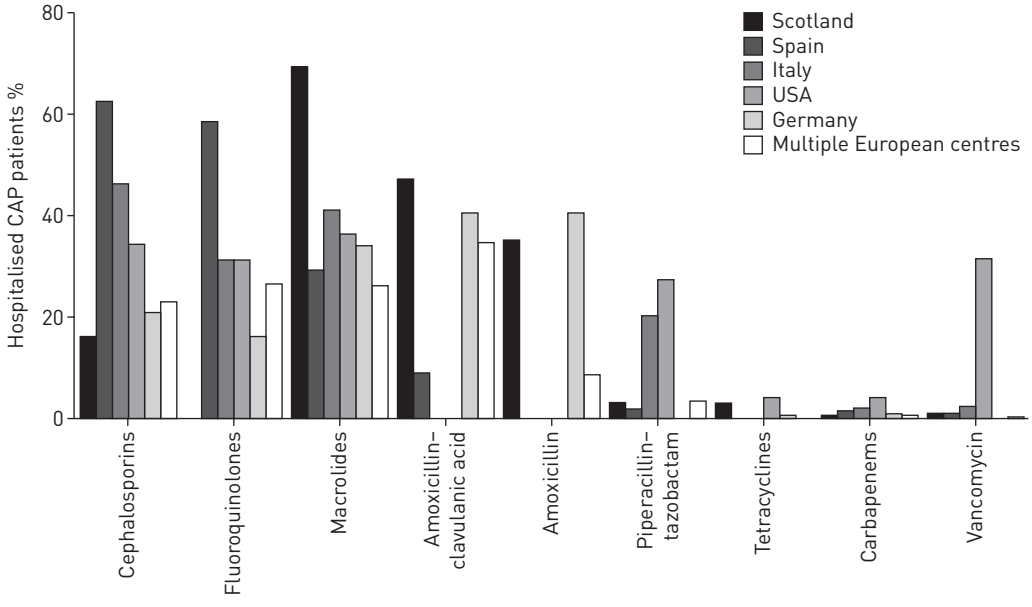

Figure 4. Empirical antibiotic usage for CAP in pneumonia cohorts from Scotland (n=1883) [67], Spain (n=1591) [67], Italy (n=935) [68], a US Dept of Veterans Affairs database study (n=95 511) [69], Germany (n=1041) (CAPNETZ (German Competence Network for CAP) study, unpublished data) and a multicentre European audit (n=2039) [70].

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of 11 days (Figure 5a and b). No association was found between severity of disease and antibiotic duration (Figure 5c) [78–80]. There was also no association with clinical response using the "time to clinical stability" criteria, suggesting that duration was largely random and unrelated to clinical need [78]. Similar data are evident in individual studies, with a mean duration of 10 days from diverse healthcare systems, including those in the UK, Switzerland and the USA [40, 81, 82].

Duration is therefore a major target for antimicrobial stewardship interventions. Guidelines incorporating PCT as a biomarker can result in a reduction of antibiotic duration of nearly

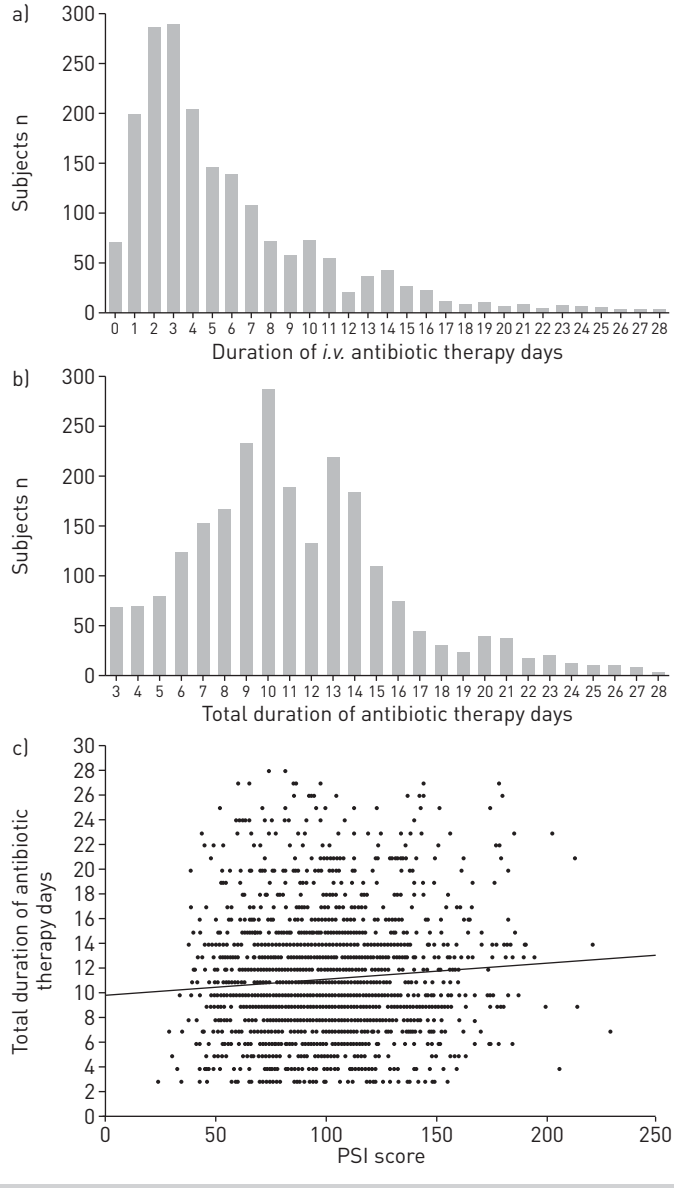

Figure 5. a) Duration of intravenous antibiotic therapy, b) total duration of antibiotic therapy, and c) association between Pneumonia Severity Index (PSI) score and duration of antibiotic therapy. Reproduced and modified from [78] with permission.

3 days in RCTs [81]. Simple antimicrobial stewardship interventions incorporating education and feedback to prescribers can achieve a similar level of reduction. For example, Avdic *et al.* [82] found a reduction in duration from 10 to 7 days by simply educating physicians on antibiotic duration and providing feedback through pharmacists to prescribers [82]. A UK study found a mean reduction in duration of 2 days with the introduction of an intervention simply consisting of automatic stop dates for antibiotics based on local guidelines [33]. None of these interventions were associated with a worse outcome. Recently, in an RCT of 312 patients, Uranga *et al.* [83] showed that antibiotics could be safely discontinued at day 5 in patients that had reached clinical stability. This is not surprising, as 10 years earlier el Moussaoui *et al.* [84] showed in an RCT that 3 days of amoxicillin was equivalent to 8 days in mild to moderate CAP patients that had reached clinical stability [84]. No such trials exist for severe CAP, where ⩾10 days of antibiotic treatment is common [85]. Choudhury *et al.* [86] demonstrated in an observational cohort study using propensity adjustment that 7 days was as least as effective as long courses even for the most severe patients.

Taken together, these data make antibiotic duration a promising target for antibiotic stewardship approaches in hospital. The optimal duration of antibiotics will need to be personalised to the individual, but appears to be 3–5 days for mild CAP and 5–10 days for severe CAP.

De-escalation is unfortunately rarely utilised in CAP. In a multicentre audit of European CAP patients from 10 countries, only 5.1% had de-escalation of therapy [70]. Carugati *et al.* [87] reported on 660 bacteraemic CAP patients from 35 countries and identified much higher rates of de-escalation (63.2%). The reasons for this high variability in practice are unknown. RCTs have been used to investigate the ability of microbiological tests to guide de-escalation. van der Eerden *et al.* [32] studied 262 patients, and used sputum Gram stain and pneumococcal urinary antigen to de-escalate therapy. Antibiotic use was reduced in the pathogen-directed therapy group, which was associated with a statistically significant reduction of 43% in antibiotic-associated side-effects. A very similar study conducted in Spain by Falguera *et al.* [88] recruited 177 patients and primarily used urinary antigen testing to target therapy. Adverse events were again reduced by 50% through a lower exposure to antibiotics with no significant differences in outcomes.

The 2016, the German–Austrian–Swiss CAP guideline recommended de-escalation of an initial β-lactam plus macrolide combination to β-lactam monotherapy after 3 days if no atypical pathogen is detected and the patients shows clinical improvement. Furthermore, de-escalation to penicillin monotherapy is recommended if pneumococci are detected by either culture or antigen test. This approach has been considered feasible as penicillin-resistant pneumococci are rare in Germany [89].

The impact of clinical guidelines

A comparison of international CAP guidelines shows that there is large variability in the method of antibiotic selection and also in the recommended empirical regimens (table 2) [60–66, 89, 90].

Multiple studies show that regardless of the international context, compliance with guideline-recommended antibiotic regimes results in improved clinical outcomes. Arnold *et al.* [92] examined an international cohort (n=1649 patients) and demonstrated that

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Table 2. International guideline recommendations for CAP

Guideline [ref.]	Method of antibiotic guidance	Recommendation
British Thoracic Society and National Institute for Care Excellence [60]	CURB-65	CURB-65 0–1: oral amoxicillin (macrolide or tetracycline if allergy) CURB-65 2: amoxicillin and macrolide CURB-65 3–5: β-lactamase-stable β-lactam and macrolide
European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases [61]	Site of care; risk factors for *P. aeruginosa*	Outpatient treatment: amoxicillin or doxycycline Inpatient (non-ICU) treatment: β-lactam with or without macrolide and respiratory fluoroquinolone Inpatient (ICU) treatment: cephalosporin and macrolide plus respiratory fluoroquinolone with or without cephalosporin
Infectious Diseases Society of America/American Thoracic Society [62]	Site of care; risk factors for specific pathogens; risk factors for antimicrobial resistance	Outpatient treatment: 1) previously healthy, no risk factors for resistant pathogens: macrolide or doxycycline; 2) risk factors for specific pathogens or antimicrobial resistance[#]: respiratory fluoroquinolone, β-lactam[¶] and macrolide Inpatient (non-ICU) treatment: respiratory fluoroquinolone, β-lactam plus macrolide Inpatient (ICU) treatment: β-lactam (cefotaxime, ceftriaxone or ampicillin–sulbactam) and either azithromycin or respiratory fluoroquinolone
Spanish Society of Chest Diseases and Thoracic Surgery [63]	Site of care; risk factors for *P. aeruginosa*	Outpatient: respiratory fluoroquinolone Inpatient: β-lactam plus macrolide ICU admission: β-lactam plus macrolide Risk factors for *P. aeruginosa*: carbapenem or piperacillin–tazobactam plus levofloxacin
Canadian Infectious Disease Society and Canadian Thoracic Society [64]	Site of care; risk factors for specific pathogens and comorbidities	Outpatient: macrolide; COPD: newer macrolide; recent antibiotics or corticosteroids: respiratory fluoroquinolone Nursing home resident: fluoroquinolone or β-lactam plus macrolide

Continued

Table 2. Continued

Guideline [ref.]	Method of antibiotic guidance	Recommendation
Brazilian Thoracic Society [65]	Site of care; risk factors for *P. aeruginosa*	Hospitalised: respiratory fluoroquinolone ICU patient: β-lactam plus respiratory fluoroquinolone Risk factors for *P. aeruginosa*: antipseudomonal cephalosporin plus fluoroquinolone Outpatient: previously healthy: macrolide monotherapy; comorbidities or recent antibiotics: respiratory quinolone Inpatient: respiratory quinolone or β-lactam plus macrolide ICU admission: β-lactam plus quinolone or macrolide Risk factors for *P. aeruginosa*: β-lactam plus quinolone
Australia [66]	SMART-COP; CORB	Nonsevere (CORB <2 or SMART-COP <5): benzylpenicillin *i.v.* plus oral doxycycline or roxithromycin Severe (CORB ⩾2 or SMART-COP ⩾5): benzylpenicillin *i.v.* plus gentamicin *i.v.* or ceftriaxone *i.v.* or cefotaxime *i.v.* plus azithromycin *i.v.*
Guideline of the German Respiratory Society, Paul Ehrlich Society for Chemotherapy, German Society for Infectious Diseases, CAPNETZ (German Competence Network for CAP), Austrian Respiratory Society, Austrian Society for Infectious and Tropical Diseases, and Swiss Respiratory Society [89]	Site of care; comorbidities	Mild without comorbidities (oral): amoxicillin (second choice: respiratory fluoroquinolone, macrolide or doxycycline) Mild with comorbidities (oral) (*i.e.* cardiac insufficiency, cerebral disorders with risk of aspiration, COPD, bronchiectasis, bedridden, percutaneous endoscopic gastrostomy): amoxicillin–clavulanic acid (second choice: respiratory fluoroquinolone) Moderate (inpatient, *i.v.*): aminopenicillin plus β-lactamase inhibitor or second/third-generation cephalosporin with or without a macrolide (second choice: respiratory fluoroquinolone) Severe (ICU): piperacillin–tazobactam or ceftriaxone or cefotaxime plus a macrolide (second choice: respiratory fluoroquinolone)

Continued

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Table 2. Continued

Guideline [ref.]	Method of antibiotic guidance	Recommendation
Japanese Respiratory Society [90]	A-DROP score; pathogen directed[+]	Mild to moderate (A-DROP 0–3): "typical": amoxicillin; "atypical": macrolide or tetracycline Severe (A-DROP 4–5): young patient: *i.v.* fluoroquinolone; elderly and/or comorbidity: third-generation cephalosporin and tetracycline or macrolide

CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years; *P. aeruginosa*: *Pseudomonas aeruginosa*; SMART-COP: predicts the need for mechanical ventilation or vasopressor support based on low systolic blood pressure, multilobar chest radiography involvement, low albumin level, high respiratory rate, tachycardia, confusion, poor oxygenation and low arterial pH; CORB: confusion (acute), oxygen saturation ⩽90%, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic); A-DROP: age (male ⩾70 years, female ⩾75 years), dehydration (urea ⩾210 mg·L^{-1}), respiratory failure (arterial oxygen saturation ⩽90% or arterial oxygen tension ⩽60 mmHg), orientation disturbance (confusion), blood pressure <90 mmHg (systolic). [#]: risk factors for resistance listed in the guidelines are presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months; [¶]: includes penicillin, aminopenicillin, aminopenicillin plus β-lactamase inhibitor and cephalosporins; [+]: Japanese Respiratory Society guidelines recommend different empirical treatment if clinically typical or atypical infections are suspected. Reproduced and modified from [91] with permission.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guideline-compliant antibiotic regimes were associated with a more rapid improvement (using time to clinical stability), shorter length of hospital stay (8 *versus* 10 days) and decreased mortality (8% *versus* 17%). In studies of patients admitted to the ICU, guideline-compliant therapies were also associated with reduced mortality. Frei *et al.* [93] found a large reduction in mortality (11% *versus* 25%) in 129 ICU patients with CAP treated according to IDSA/ATS guidelines. Several studies have shown similar results internationally [94, 95]. These studies have limitations inherent to observational research, including that younger, less comorbid patients are more easily recognised as pneumonia and therefore more easily treated with the guideline-concordant regimes [96].

As well as having a positive effect on antibiotic practices, guidelines can have a negative effect on antimicrobial stewardship if they recommend excessive or unnecessary antibiotic treatment [97]. The 2005, the ATS/IDSA guidelines for HAP and VAP created a new category of pneumonia designated "healthcare-associated pneumonia" [97, 98]. This group, which includes patients with hospitalisation in the previous 3 months, nursing home residents and other patients with frequent healthcare contacts, was recommended to receive broad-spectrum therapy including coverage of MRSA and *P. aeruginosa* [97, 98]. The evidence base for this recommendation at the time was limited and subsequent data have demonstrated no benefit of broad-spectrum coverage in this patient population [99, 100]. Indeed, a prospective cohort study has shown that adherence to triple therapy ("double Gram-negative coverage" plus MRSA coverage) was associated with a significant decrease in

survival. Patients with a lower risk for MDR pathogens (*e.g.* no prior antibiotic treatment, shorter hospital stay and younger age) were harmed by this therapy [101].

Despite this, a large rise in prescribing of broad-spectrum antibiotics and an increased use of vancomycin has been observed in the USA and elsewhere since the introduction of the ATS/IDSA guidelines in 2005 [69]. Jones *et al.* [69] showed in more than 95 000 patients that vancomycin use doubled after 2005 from 16% to 31% in 2010, while antipseudomonal use also doubled from 5% to 11% over the same period. A prospective analysis of the EPIC (Etiology of pneumonia in the community) cohort commissioned by the Centers for Disease Control and Prevention in the USA (n=2259) showed 30% of CAP patients received empirical therapy directed against MRSA, despite a rate of MRSA in this population of only 0.7% [102].

Guidelines writers therefore have a key responsibility to balance the need to cover all possible pathogens with the potential harmful consequences of excessive broad-spectrum prescribing at the population level (table 3) [103–105].

Antimicrobial stewardship in the ICU

Optimal antibiotic use in critically ill patients is essential because of the combination of a patient population at exceptionally high risk of death and the very high risk of antibiotic-resistant pathogens encountered in mechanically ventilated patients [106–108].

Studies suggest between one- and two-thirds of antibiotics prescribed in the ICU are inappropriate. Thus, the priorities in the ICU are the rapid identification of patients with bacterial infection, the rational choice of antibiotic treatments, appropriate dosing, de-escalation and appropriate duration of treatment [109]. The principals of antimicrobial stewardship described above can therefore be clearly applied to respiratory infections in the ICU.

Table 3. Key recommendations for antimicrobial stewardship in CAP[#]

- Hospitals should have clear guidelines for antibiotic use in CAP, supported by feedback to prescribers and systems to monitor antibiotic use
- Prescribe empirical antibiotic treatment according to CAP guidelines, using the narrowest spectrum necessary
- Request microbiological tests to establish the cause of CAP, including blood/sputum cultures, urinary antigen tests and PCR where available
- Prescribe oral antibiotics in mild to moderate CAP patients that are able to swallow; switch from intravenous to oral antibiotics as soon as possible after admission
- Prescribe a treatment duration of 5 days for mild to moderate CAP and 7 days for severe CAP, modified as required according to treatment response; use prescriber feedback and automatic stop dates to monitor antibiotic duration
- De-escalate therapy based on the results of microbiological testing; in particular, detection of pneumococci can initiate de-escalation to penicillins
- Review the diagnosis of CAP and stop antibiotics if a noninfective cause of respiratory symptoms is identified as a result of further testing

[#]: these broad principles are equally applicable to many respiratory infections.

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Initial antibiotic prescribing should not be delayed in patients with suspected sepsis or septic shock, as earlier therapy may reduce mortality [110]. Nevertheless, as major trauma, surgery, acute respiratory distress syndrome, transplant rejection and multiple other noninfectious disorders may be mistaken for infection in the ICU, it is essential to regularly review whether antibiotics are necessary. Knowledge of the local prevalence of antibiotic-resistant pathogens and local antibiotic policies are needed as healthcare-associated infections in the ICU may be associated with organisms such as *P. aeruginosa*, *Enterobacteriaceae* (which may include ESBL-producing organisms or carbapenemase-producing organisms in some healthcare environments) and MRSA [111]. Epidemiological surveillance is therefore vital. Judicious use of carbapenems, broad-spectrum β-lactams and anti-MRSA drugs is necessary to limit the spread of antibiotic resistance.

A systematic review of de-escalation interventions showed that they can be readily performed, but that evidence on the impact of de-escalation on outcomes is poor [112]. The general advice is that if patients have received broad-spectrum treatment empirically, if blood and respiratory tract cultures subsequently return negative or if an organism sensitive to narrower therapy is isolated, then de-escalation should be performed. An example is discontinuing linezolid or vancomycin where MRSA is not isolated.

Duration of therapy for VAP is often prolonged, as relapse rates are high for organisms such as *P. aeruginosa* and *Acinetobacter* spp. An RCT of 8 *versus* 15 days for VAP showed no difference in clinical outcomes [113]. Clinicians are often not keen to use shorter courses, however, preferring the reassurance of an objective measure of treatment response [106]. De Jong *et al.* [114] recently reported the impact of PCT on antibiotic duration in critically ill patients. This Dutch trial (n=1575) in 15 hospitals found a reduction in duration from a median of 7 to 5 days ($p<0.0001$) with, surprisingly, a reduction in mortality (25% *versus* 20%) in favour of PCT guidance. This reduction was not observed in the earlier PRORATA (Impact of PCT to reduce antibiotics use in ICU adult patients) trial, which had used similar PCT values as stopping triggers (decrease by 80% of the peak value or <0.5 ng·L^{-1}) but found a nonsignificant increased mortality in the PCT arm [115]. In contrast to the PRORATA trial, physicians were not forced to de-escalate. This may suggest that PCT helps physicians to discontinue unnecessary antibiotics in stable patients [115].

No single measure can provide a solution to the complex needs of critically ill patients and so, as with other aspects of critical care medicine, care bundles have been developed for antimicrobial stewardship. Some of the potential components of antimicrobial stewardship interventions in critically ill patients with respiratory infections are shown in table 4.

Antimicrobial stewardship in acute exacerbation of COPD and asthma

The role of antibiotics in exacerbations of airways disease will not be considered in detail here as it is covered in a separate chapter of this *ERS Monograph* [116].

Antimicrobial stewardship principles apply equally to exacerbations of airway disease as they do in CAP. The majority of asthma exacerbations are viral and do not require antibiotic therapy [117–120]. A recent large RCT of antibiotics in asthma exacerbation reported no clinical benefits, and so in the absence of CAP or another indication for antibiotic treatment, antibiotic prescribing should be withheld [121].

Table 4. Antimicrobial stewardship principles as applied to respiratory infections in the ICU

Intervention	Discussion
Early empirical antibiotic treatment	Particularly for patients with sepsis and septic shock, early empirical antibiotic administration is necessary and should be tailored to local microbiological surveillance data
Comprehensive microbiological testing	To include BAL, blood cultures and other samples as appropriate to suspected infection; these allow de-escalation at a later time point if empirical treatment is started
Daily review of antibiotic prescribing	Alternative diagnoses may emerge during admission; antibiotics should be discontinued if VAP or other respiratory infections become unlikely, or an alternative diagnosis is identified
Pharmacokinetic/pharmacodynamic optimisation of dosing	Ensures appropriate doses are used and reach the site of infection
De-escalation of treatment	Narrower therapy if non-MDR pathogens are identified or if all cultures are negative
Treat for the shortest necessary duration	Discontinue antibiotics at 7–10 days provided clinical response is adequate within this time period; use of biomarkers (CRP, PCT) can help facilitate these decisions, but is not a replacement for good antibiotic practice and guidelines
Microbiology support and review	Antibiotic prescribing decisions are shared with critical care physicians and infection specialists (infectious disease, respiratory, microbiology) to ensure rational prescribing

For exacerbations of all airway disease, antibiotics should be given for the shortest duration necessary and 5 days appears to be effective for the majority of cases where antibiotics are required. De-escalation may be necessary if broad-spectrum antibiotics are initially prescribed and, in particular, in the rare cases that *P. aeruginosa* is empirically treated (*e.g.* in severe COPD with prior *P. aeruginosa* isolation) [122]. In these cases, sending sputum samples at admission and using these for de-escalation seem reasonable. Sputum cultures may be misleading in severe COPD as patients are often chronically colonised with *H. influenzae*, *Moraxella catarrhalis* or other Gram-negative bacteria [123, 124]. As these organisms can be isolated when clinically stable, their presence in sputum at exacerbation does not necessarily imply acute infection and their presence after antibiotic treatment does not necessarily mean the requirement for ongoing treatment.

Antimicrobial stewardship in exacerbation of bronchiectasis or cystic fibrosis

There are limited data on the role of antimicrobial stewardship in these disorders where the liberal use of antibiotics is considered the norm [125, 126]. Bronchiectasis is becoming increasingly common and consequently an increasingly important group of patients in terms of antibiotic consumption. The optimal duration of treatment for exacerbations is not known, but has been identified as a key research priority [127]. Appropriate antibiotic treatment can be supported by sending sputum samples when clinically stable, to identify

 https://doi.org/10.1183/2312508X.10017616

the antibiotic most likely to be effective and reduce the need for multiple broad-spectrum drugs at exacerbation. Patients should also have sputum samples sent at exacerbation to modify treatment as needed if new pathogens are isolated [128].

Prevention of infections

It should be noted that an important principal of stewardship is the avoidance of the need for antibiotics in the first place. A comprehensive plan to reduce overall antibiotic consumption should include measures to reduce the incidence of LRTIs. This includes addressing modifiable risk factors, such as aspiration risk factors and unnecessary inhaled corticosteroids in patients with COPD for pneumonia [47, 129–131]. Providing pneumococcal and influenza vaccination may also reduce hospitalisations for LRTIs [132–134].

Prevention also means optimally managing patients with COPD, bronchiectasis, asthma and cystic fibrosis, with nonantibiotic pharmacotherapy and physiotherapy interventions that then reduce the need for antibiotic treatment [135, 136].

Conclusions

Antimicrobial stewardship principles apply to all of the common respiratory disorders presented to hospital. Data suggest international antibiotic practices for many respiratory infections are excessive, and can be improved through systematic application of good prescribing practices, guidelines and feedback interventions.

Table 5. Proposed research questions for antimicrobial stewardship in respiratory infections

CAP
- Is the diagnosis correct?[#]
- Which patients with CAP require macrolides/atypical coverage?
- Can pathogen-directed treatment (using molecular techniques or urinary antigen tests) reduce antibiotic use or duration?
- Can treatment response markers (CRP, PCT, clinical stability criteria) be used to stop antibiotics?
- What is the optimal method (scoring systems and molecular techniques) for identifying MDR pathogens in CAP?
- Are biomarker-guided approaches to reducing antibiotic duration cost-effective compared with simple antimicrobial stewardship interventions such as education and feedback?

Acute exacerbation of COPD/asthma
- What is the optimal method for identifying patients with acute exacerbation of COPD likely to respond to antibiotics?
- Do antibiotics reduce time to next exacerbation rather than improving early clinical outcomes?
- What is the role of molecular microbiology techniques in identifying bacterial infection?

Acute exacerbation of bronchiectasis/cystic fibrosis
- What is the optimal duration of antibiotics for exacerbations?

Critical care medicine
- Can point-of-care diagnostics more accurately diagnose VAP?
- What is the best biomarker to use for de-escalation of therapy?
- What is the optimal duration of therapy for VAP?

[#]: most nonpneumonia LRTIs do not require antibiotics.

Incorporating antimicrobial stewardship principles into the daily practice of respiratory physicians worldwide can significant improve patient outcomes while combating antibiotic resistance. Proposed research questions for antimicrobial stewardship in respiratory infections are listed in table 5.

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Disclosures: J.D. Chalmers has received grants from Aradigm, AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, GSK, Novartis and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, Chiesi, Napp and Pfizer. M.W. Pletz has received grants from the German Research Foundation, the German Ministry for Science and Education, Biotest, InfectoPharm and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Biotest, Clinigen, InfectoPharm, MSD, Pfizer and Thermo Fisher, and has a patent ¨Measuring antibiotic blood levels with Raman spectroscopy¨ pending.

Chapter 9

Antibiotics in acute exacerbation of asthma and COPD

Gernot G.U. Rohde

This chapter covers the difficult topic of antibiotic treatment of exacerbations of asthma and COPD. It gives an overview of the current understanding of the microbiology involved in the two very different diseases and their exacerbations, and introduces the most relevant clinical trials performed so far. The appraisal of the microbiology and the studies will hopefully help clinicians to make educated treatment choices based on the current literature. Moreover, ongoing trials are presented in order to highlight the directions in which the field is evolving.

Cite as: Rohde GGU. Antibiotics in acute exacerbation of asthma and COPD. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 150–158 [https://doi.org/10.1183/2312508X.10005116].

This is a difficult topic with much less evidence than one might think. However, let us begin at the beginning. Respiratory tract infections are among the most important reasons for hospitalisation in adults [1]. On the one hand, the introduction of antibiotics has probably saved millions of lives. On the other hand, inappropriate use and overuse leads to increased antibiotic resistance [2, 3] and increased complications, such as healthcare-associated infections (*e.g. Clostridium difficile* infection).

A retrospective cohort study identified that antibiotics were prescribed in 85% of 69 820 patients admitted for acute exacerbation of COPD (AE-COPD) to 360 hospitals throughout the USA [4]. A recent prospective clinical study confirmed this by showing that 79% of patients hospitalised for COPD and 59% patients hospitalised for asthma exacerbation received antibiotic treatment, while only 25% and 5% of these patients, respectively, showed evidence of bacterial infection [5]. Another comparable study investigating 842 patients hospitalised for acute respiratory tract infection found evidence for bacterial infection in 12%, for viral infection in 25% and for mixed infection in another 16% of patients [1]. No microbiological diagnosis was obtained in the remaining 47% of patients. The primary clinical diagnoses were AE-COPD, pneumonia, acute bronchitis and asthma exacerbation. 90% of the viral and 92% of the mixed infections were treated with antibiotics, and four of

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the 10 deaths among patients hospitalised with viral infection alone were secondary to complications of *C. difficile* colitis [6].

Evidence suggests that a significant proportion of hospitalisations are actually primarily viral in origin [7–9]. Moreover, it seems that antibiotics are continued if started at admission in the majority of patients with viral detection and normal chest radiograph, which may represent inappropriate use [10].

Regarding the situation in asthma attacks, a very recent study screening more than 4500 patients with acute asthma attacks could only randomise 199 from a planned 380 patients because most patients had already received antibiotic treatment [11].

Therefore it makes sense to look a little closer at the microbiological aetiology of acute exacerbations of asthma and COPD.

Microbiological aetiology of acute exacerbations of asthma and COPD

Asthma

Several studies from the 1970s indicated the difficulty in detecting bacterial infection in patients with asthma exacerbations [12]. Clarke [13] followed 51 patients over 18 months and identified 111 exacerbations. He obtained sputum only from eight exacerbations and four of these yielded positive culture results (*Haemophilus influenzae* in three and *Staphylococcus aureus* in one). In the same decade, Berman *et al.* [14] performed a study on 27 asthma patients and 12 healthy control subjects using transtracheal aspirates. Again, in this very invasive study avoiding contamination from the upper airways, no correlation was found between detection of bacterial pathogens and asthma exacerbations [14]. Detection of pathogens might have been hampered at that time by the detection methods, which were mainly culture dependent.

A recent study from Japan reported microbiological data from 50 asthma patients admitted to hospital using culture-independent multiplex PCR analysis to detect 15 major respiratory viruses and five bacteria (including atypical bacteria, *Streptococcus pneumoniae* and *H. influenzae*) in nasopharyngeal swabs [15]. In addition, conventional sputum culture was performed. 20 stable asthma patients without any asthmatic attack in the previous year and without recent respiratory infection represented the control group. 48 (96%) of the acute patients had a common cold before presentation, their mean age was 58 years and 66% were current or ex-smokers, whereas only 5% of stable patients were smokers. Pathogens were detected in 70.8% of the acute patients and in 75% of the stable patients, with viral detection in 52.1% and 50% and bacterial infection in 37.5% and 30%, respectively. COPD (16%) and pneumonia (6%) were reported as comorbidities. Clearly this study does not allow conclusions on the microbiology as there are important reservations about the high detection rate in controls and the clinical phenotype of the asthma patients when considering their comorbidity profile.

A study aiming to define the microbial aetiology in adults hospitalised for an acute exacerbation of chronic cardiopulmonary illness (including exacerbations of COPD, asthma and congestive cardiac failure) or an acute pulmonary illness (including pneumonia, bronchitis and influenza-like illness) revealed interesting insights [5]. 780 patients were

enrolled during three consecutive winter seasons. Blood cultures, sputum cultures, urinary antigen tests and molecular testing for viruses using multiplex PCR of nasopharyngeal samples were performed. Bacteria and viruses were detected in 19% and 44%, respectively, of patients with an acute respiratory illness. Bacteria were most frequently detected in patients with pneumonia (33%) and exacerbation of COPD (25%). *S. pneumoniae* was the most frequently detected bacterial pathogen (53% of patients with positive tests for bacteria). Only 5% of the patients hospitalised with exacerbation of asthma tested positive for bacteria, which increased to only 9% in patients with an adequate sputum sample. In contrast to these findings, 59% received antibiotic therapy. Comparably, a study from Australia found a bacterial detection rate of 5% in patients presenting to the emergency department with exacerbation of asthma [16]. The viral detection rate was 32%.

The literature on atypical bacteria infections (*e.g. Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*) in asthma is also very heterogeneous. A systematic review reported detection rates of 3.5% (0–4%) and 18% (0–73%), respectively [17]. However, in many studies the detection rates were not higher in patients with asthma exacerbations compared with controls so that the conclusion was "atypical bacteria seem to be inconsistently associated with asthma exacerbations. This could be explained by suboptimal detection and/or it could be because of significant temporal variability" [17]. In addition there is a diagnostic dilemma as often serological evidence of infection cannot be confirmed by PCR [18]. However, using PCR as a reference standard also has its limitations. A study from Finland using PCR to detect rhinovirus, *Chlamydia* (*Chlamydophila*) and *Bordetella* found that *C. pneumoniae* PCR was positive in 37% of healthy controls, 21% of mild asthma patients and 22% of moderate asthma patients [19]. *Bordetella pertussis* PCR was positive in 17% of healthy controls, 28% of mild asthma patients and 20% of moderate asthma patients. Hence, the true prevalence and the pathogenetic role are difficult to assess.

COPD

We have a much better understanding of the airway microbiology in COPD. In one of the sentinel studies, Sethi *et al.* [20] followed 81 COPD patients in detail at monthly intervals over 4.5 years. Clinical symptoms and signs as well as sputum and serum samples were obtained at each visit. An exacerbation was present in 23.6% of visits at which pathogens were isolated from sputum compared with 18.0% of visits without pathogens, resulting in a significantly increased relative risk of an exacerbation for patients with pathogens. Importantly, at the individual bacterial species level this was only significant for isolation of *Moraxella catarrhalis* and *S. pneumoniae*, and not *H. influenza* or *Pseudomonas aeruginosa* and Gram-negative bacilli. However, molecular typing of pathogens revealed that isolation of a new strain of a pathogen (including *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, but not *P. aeruginosa*) was associated with a significant increase in the frequency of exacerbation.

Another 1-year prospective study of 373 patients hospitalised with AE-COPD in Hong Kong revealed only low growth rates of bacterial cultures (*H. influenzae* 13.0%, *P. aeruginosa* 6.0% and *S. pneumoniae* 5.5%) [21].

Well-designed studies using the protected specimen brush technique confirmed, however, that indeed one-quarter of stable COPD patients are colonised with "potentially pathogenic

 https://doi.org/10.1183/2312508X.10005116

microorganisms" [22]. During exacerbation, only *P. aeruginosa* was associated with exacerbation symptoms, although this was independent of the bacterial load and was mainly observed in very severe exacerbations necessitating mechanical ventilation [22].

Clark *et al.* [5] reported a bacterial detection rate of 25% in patients hospitalised for COPD exacerbation (43% in patients with sputum culture performed). 79% of all hospitalised COPD patients received antibiotic treatment. Interestingly, although 38% of patients tested positive for respiratory viruses (mainly influenzavirus, picornavirus and respiratory syncytial virus), no patient received antiviral treatment.

Papi *et al.* [23] investigated 64 patients hospitalised for COPD exacerbation and found positive bacterial cultures in 35 (54.7%) sputum samples during exacerbations: nine *H. influenzae*, eight *S. pneumoniae*, seven *M. catarrhalis*, four *S. aureus*, four *P. aeruginosa* and three *Enterobacter* spp.; 24 (37.5%) positive bacterial cultures were obtained in convalescence: six *H. influenzae*, five *S. pneumoniae*, four *M. catarrhalis*, four *S. aureus*, three *Enterobacter* spp. and two *P. aeruginosa* ($p=0.08$ *versus* exacerbations).

Domenech *et al.* [24] followed 111 severe and very severe COPD patients (forced expiratory volume in 1 s (FEV_1) <50%) over 1 year and recorded 224 episodes of AE-COPD. 170 out of 188 (90.4%) good quality sputum samples were culture positive, whereas 42 out of 188 (22.3%) were positive for more than one pathogen. No samples were taken during the stable state as the study investigated the differences between patients with one and more than one exacerbation. They found that *P. aeruginosa* was the most frequent pathogen in both groups of patients, whereas *H. influenzae* was associated with patients with a single annual AE-COPD and members of the *Enterobacteriaceae* were associated with frequent exacerbators. Of note, nearly half of the patients developed bronchiectasis.

Culture-dependent detection of airway bacteria might be limited by the low sensitivity of the methods and therefore culture-independent methods such as real-time PCR have been used. Garcha *et al.* [25] analysed 373 sputum samples from 134 COPD outpatients for prevalence and load of typical airway bacteria (*H. influenzae*, *S. pneumoniae* and *M. catarrhalis*) using multiplex quantitative PCR and found bacteria significantly more frequently by PCR (59.3%) compared with culture (24.3%). Bacteria were also more prevalent during exacerbation (56.5%) compared with the stable state (44.2%), with a 10-fold higher bacterial load as analysed by PCR. Bronchiectasis was not excluded in this study. Using this new technique, it seems that bacteria can also be detected during the stable state in nearly half of all COPD patients, and that increases in frequency and load are limited. A recent study correlated bacterial detection (76.7% positive samples by PCR) to local inflammation, and showed a good correlation between the presence of *H. influenzae* and IL-1β, IL-8, IL-10, TNF-α and symptoms at the stable state, but not during exacerbation [26]. Bronchiectasis was present in nearly 20% of patients undergoing a CT scan. Although promising, many questions remain about PCR, mainly the relevance of the high detection frequency and lack of correlation to exacerbations.

Summary

In summary, we can conclude that bacterial infection including atypical bacteria is very infrequent in asthma exacerbations. In COPD, the high frequency of bacterial detection during the stable phase, often referred to as colonisation, makes it difficult to establish

bacterial infection as a trigger of exacerbations despite the fact that well-designed studies have shown that a switch of the colonising strains precedes exacerbation and the weak evidence of increased bacterial load during exacerbations. Nevertheless, antibiotics are very frequently prescribed for both entities. Therefore, let us consider the evidence for the potential effectiveness of antibiotics in asthma and COPD exacerbations.

Clinical trials

Asthma

Treatment of exacerbations

There is not a lot of evidence on this subject. The latest Cochrane analysis of antibiotics for acute asthma dates back to 2001 [27]. At that time only two placebo-controlled studies were identified. The antibiotics investigated were ampicillin and hetacillin, and there were no significant effects on healthcare utilisation or lung function. An update of the initial search in 2005 yielded no new results [27].

A later trial using roxithromycin for 6 weeks in patients with stable asthma led to a significant improvement in evening peak expiratory flow at the end of treatment, but the difference between the groups diminished thereafter [28]. The symptom score was not significantly improved.

Another randomised double-blind placebo-controlled trial using clarithromycin for 6 weeks in stable asthma outpatients showed a significant improvement in FEV_1 in *Mycoplasma*/*Chlamydophila* PCR-positive subjects only [29]. However, only one-third of these patients received inhaled corticosteroids. A subsequent placebo-controlled trial was performed to evaluate the effect of 16 weeks of clarithromycin treatment, added to fluticasone, on asthma control in individuals with or without lower airway PCR evidence of *M. pneumoniae* or *C. pneumoniae* [30]. No further improvement of asthma control could be demonstrated.

The Telicast study investigated 278 patients with acute asthma exacerbations randomised to either 800 mg telithromycin or placebo for 10 days [31], and found an improvement in symptoms and in lung function tests performed in the clinic, but not in home-measured peak expiratory flow rates. The authors could not prove antibiotic effects as the underlying mechanism.

The most recent study, the AZALEA (Azithromycin against placebo in exacerbations of asthma) RCT, investigated the effect of azithromycin, 500 mg daily for 3 days, on top of standard treatment for asthma attacks [11]. 380 patients were needed to detect a significant change in the primary outcome (diary card symptom score 10 days after randomisation). More than 4500 patients were screened, but only 199 patients could be randomised during nearly 3 years of screening. The most frequent reason for screening failure was pre-treatment with antibiotics. The outcome of the study was that antibiotic treatment with azithromycin resulted in no statistically or clinically significant benefit [11].

Despite these findings, it was recently reported that one-third to more than half of asthma patients receive at least one course of respiratory antibiotics in primary care (in the UK and France) [32].

 https://doi.org/10.1183/2312508X.10005116

Prevention of exacerbations

In a randomised double-blind placebo-controlled trial in patients with severe asthma, add-on treatment with low-dose azithromycin for 6 months did not decrease the frequency of the severe exacerbations of asthma and/or LRTI requiring antibiotics [33]. However, in subjects with severe noneosinophilic asthma, add-on treatment with azithromycin was associated with a significant reduction in these end-points and in the rate of severe exacerbations. Azithromycin improved quality of life and was well tolerated [33].

COPD

The most recent Cochrane review assessing the effects of antibiotics in the management of AE-COPD on treatment failure and important patient outcomes (mortality, adverse events, length of hospital stay) dates back to 2012 [34]. 16 clinical trials with 2068 participants were included. For outpatients (mild to moderate exacerbations) the review revealed a 25% reduction in risk of treatment failure between 7 days and 1 month after treatment initiation. However, the quality of the evidence was rated as low and, after restriction of the analysis to currently available drugs, no significant reduction was observed anymore. Looking closer at the results, only the most recent trial showed a benefit of antibiotic treatment and drove the results towards the beneficial effects of antibiotics [35]. In this trial, as in most of the other trials included, there was no predefined standard treatment of AE-COPD including systemic corticosteroids, which makes a considered analysis of the added value of antibiotics on top of current standard treatment impossible.

Previously, Sachs *et al.* [36] performed the only randomised double-blind controlled trial investigating the effects of antibiotics (amoxicillin or cotrimoxazole) on top of a standard treatment with corticosteroids in patients with mild COPD exacerbations. The analysis of the primary end-point was improvement of peak expiratory flow and symptom scores did not reveal any significant differences.

One of the most well-known trials in this field is the study from Anthonisen *et al.* [37]. This was a prospective double-blind placebo-controlled trial over 3.5 years including patients >35 years with a clinical diagnosis of COPD, defined by FEV1 <70%, Tiffenau index <70% and total lung capacity >80% of predicted values. All patients received a standard treatment of oral theophylline and albuterol, and flu vaccination; corticosteroids were continued. 173 patients, mainly suffering from severe COPD, with a total of 362 evaluable exacerbations were investigated. 182 exacerbations were treated with verum (either trimethoprim–sulfamethoxazole 960 mg twice daily, amoxicillin 250 mg four times daily or doxycycline 100 mg once daily) and 180 exacerbations were treated placebo. Patients were seen every 3 days during exacerbations. The primary outcome was clinical success within 21 days defined as resolution of all symptoms that accompanied the exacerbation. The primary outcome was reached in 55% of the placebo group and in 68% of the verum group ($p<0.01$). Anthonisen *et al.* [37] defined three types of exacerbations based on the major symptoms of increased dyspnoea, sputum volume and sputum purulence. If all symptoms were present, this was called a type 1 exacerbation; if two were present, a type 2; and if only one was present in combination with other minor symptoms, a type 3. When stratifying treatment success by type of exacerbation, antibiotic treatment was successful in 60%, 46% and 18% of type 1, 2 and 3 exacerbations, respectively. Of note, placebo was successful in 52%, 36% and 11% of type 1, 2 and 3 exacerbations, respectively. Hence, the benefit of antibiotic was very small. A major criticism is the fact that most of

the patients in this trial did not receive systemic corticosteroids during exacerbation, which makes the analysis of a possible added value of antibiotic treatment difficult.

A significant reduction of the risk of treatment failure in severe COPD exacerbations (hospital admission without ICU) was observed in the Cochrane review [34], independent of restriction to current drugs. The quality of these studies was rated as high. However, the same limitation applies to these studies, *i.e.* the lack of predefined standard treatment. Only the study from Daniels *et al.* [38] investigated the effects of antibiotics (doxycycline) on top of a standard treatment including systemic corticosteroids and found no positive effect on the primary end-point (clinical success on day 30).

There is one study from Tunisia on COPD exacerbations admitted to the ICU, which investigated the effects of ofloxacin on treatment failure in 93 ventilated patients [39]. It showed a 80% risk reduction and was rated as high quality. Nevertheless, ofloxacin is not recommended as an antibiotic for the treatment of COPD exacerbations. None of the patients in this trial received systemic corticosteroids.

Only four trials in the Cochrane review [34] addressed mortality as an end-point without significant effects. Length of hospital stay was also not improved by antibiotic treatment. Importantly, adverse events (mainly diarrhoea) were significantly more frequent in the antibiotics. Consequently, the Cochrane authors reasoned that the results were inconsistent for outpatients and inpatients, but obviously this reasoning should also be extended to ICU patients.

At present it is impossible to judge the benefit of antibiotic treatment in addition to standard treatment of AE-COPD [40].

Ongoing placebo-controlled trials

The ABACOPD study (Randomised double-blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate AE-COPD; ClinicalTrials.gov, trial number NCT01892488) [40] is the first multicenter noninferiority trial comparing prospectively and double-blinded placebo with antibiotic treatment (aminopenicillin with β-lactamase inhibitor). Inclusion is scheduled until April 2017 and hopefully the study will provide better evidence on the efficacy of antibiotic treatment during COPD exacerbations.

The AEPOC-ATB study (Antibiotic or not in nonpurulent exacerbations of COPD: a trial of security and efficacy; ClinicalTrials.gov, trial number NCT01091493) is a double-blinded, randomised placebo-controlled trial of moxifloxacin to investigate the efficacy of treatment without antibiotics in nonpurulent exacerbations of COPD. The study is being performed at four Spanish sites. The study has an estimated completion date of December 2017.

Conclusions

Most antibiotics are prescribed in primary care [41]. We have seen that most asthma exacerbations are viral in origin and that the role of bacterial infection is still debated in COPD exacerbations. It is interesting to see that no clear distinction is still being made between asthma and COPD exacerbations in primary care, and that prolonged expiration,

 https://doi.org/10.1183/2312508X.10005116

wheezes and diminished breath sounds, among others, predict the prescribing of antibiotics in both "presentations" [42]. It is clear that better diagnostic and therapeutic algorithms are needed in order to reduce inappropriate antibiotic prescribing.

At least in hospitalised patients, biomarker-guided antibiotic therapy using CRP and/or PCT has been proven to significantly reduce unnecessary antibiotic prescriptions for both asthma and COPD exacerbations [43, 44].

Clearly, we need to better understand the role and potential added benefit of antibiotic treatment in COPD exacerbations. At this moment there is no indication for antibiotic treatment of asthma exacerbations.

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Disclosures: G.G.U. Rohde has received personal fees for lectures, including services on speaker's bureaus, from Pfizer, Boehringer Ingelheim, Solvay, GSK, Essex Pharma, MSD and Novartis. He has also received personal fees for travel, accommodation and meeting expenses from GSK.

 https://doi.org/10.1183/2312508X.10005116

Chapter 10

Antifungals in pulmonary infections: to whom, when and how?

Sebastian R. Ott

The incidence of invasive fungal infection is increasing worldwide, and pulmonary infections in particular have become a major clinical challenge and threat to patients at risk. Most fungal pathogens causing pulmonary infections in humans are ubiquitous in the environment and inhalation is the most common route of acquisition, although pulmonary involvement in disseminated infections originating from other foci may occur. This chapter provides an overview on current diagnostic approaches and therapeutic strategies for the most common pulmonary fungal infections. Effective host defence against pulmonary fungal infections strongly depends on an efficient interaction between different parts of the innate and acquired immunity. Therefore, patients with innate and/or acquired/drug-induced impairment of the immune system and critically ill patients are at highest risk. Furthermore, genetic variations and polymorphisms of genes encoding for different constituents of the immune system seem to increase an individual's susceptibility to fungal infections. The clinical and radiographic appearance of most pulmonary fungal infections is nonspecific. Hence, histological and/or culture proof of fungi from samples taken from affected tissue is required to confirm the diagnosis. Non-culture-based assays and PCR from blood and respiratory samples, particularly BAL fluid, may further facilitate diagnostic efforts and accuracy. Various therapeutic strategies have been implemented for prophylaxis and treatment of pulmonary fungal infections. However, mortality remains considerably high, particularly if initiation of antifungal treatment is delayed. Treatment may be further complicated by inherent and acquired resistance to commonly used antifungals.

Cite as: Ott SR. Antifungals in pulmonary infections: to whom, when and how? *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 159–184 [https://doi.org/10.1183/2312508X.10005316].

Over recent years, the incidence of severe and invasive fungal infections has increased worldwide. With an estimated 2 million new infections every year, invasive fungal diseases have became a major clinical challenge and a threat to patients with innate or acquired/drug-induced impairment of their immune system and critically ill patients [1].

Recent advances in the treatment of malignant diseases with the widespread availability and use of multiple chemotherapy options together with the introduction of new immunosuppressive

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

drugs for autoimmune diseases, the increased number of recipients of haematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT), and critically ill patients in the ICU have increased the number of patients at risk for opportunistic infection caused by fungi and other organisms that usually have low virulence in immunocompetent patients [1, 2]. These patient groups are all characterised by an impairment of their defence towards infection; the presence of impaired phagocytosis and reduced activity of macrophages, neutropenia, dysfunction of T-lymphocytes, humoral immunodeficiency and invasive devices such as vascular catheters or endotracheal tubes may all contribute to a weakening of the individual defence mechanisms [3–5]. Additional risk factors for fungal infections include previous and uncritical treatment with broad-spectrum antibiotics, parenteral feeding and being at the extremes of age (the elderly and pre-terms/newborns). Therefore, the immune status of the respective host remains the crucial element in the susceptibility to and the presentation and progression of pulmonary fungal infections. Various underlying diseases and conditions have been identified to be associated with an increased susceptibility to invasive fungal diseases; a summary of the most important risk factors for pulmonary infections with the most frequent fungal pathogens is provided in table 1.

Candida, *Aspergillus*, *Cryptococcus* and *Pneumocystis* spp. are the leading fungal pathogens in invasive fungal diseases [6, 7]. In critically ill patients and recipients of abdominal SOT, *Candida* is the most commonly isolated fungus, mainly as a cause of bloodstream infections, and less frequently intra-abdominal infections after complicated abdominal surgery and deep-seated organ infection following SOT, both with and without candidaemia. However, despite frequent detection from respiratory samples, mainly in critically ill patients, *Candida* pneumonia is an extremely rare occurrence in non-neutropenic individuals. Detection of *Candida* from the respiratory tract most frequently indicates airway colonisation and less commonly pulmonary involvement in disseminated systemic infection rather than true fungal pneumonia regardless of the isolated species and should never automatically prompt initiation of antifungal treatment [8, 9]. In contrast, *Aspergillus* is the dominant mould in pulmonary fungal infections accounting for >85% of all invasive fungal diseases, especially in haematological patients and SOT recipients, and has increasingly also been observed in patients with exacerbated COPD and systemic steroid treatment [10, 11]. Due to the widespread use of antiretroviral

Table 1. Typical host factors associated with the most common pulmonary fungal infections

Pathogen	Host factor
***Aspergillus* spp.**	Neutropenia; allogeneic HSCT; prolonged use of systemic corticosteroids; T-cell immunosuppressants; ICU admission; SOT; severe liver disease; COPD; known chronic and subacute aspergillosis; pulmonary comorbidity (*e.g.* previously treated TB, NTM infection, COPD, bronchiectasis, sarcoidosis and lung cancer); genetic variations and polymorphisms
Pneumocystis jirovecii	HIV infection with $CD4^+$ count <200 cells·μL^{-1} and without PCP prophylaxis; primary immune deficiencies; immunosuppressive treatment for connective tissue disorders, vasculitis or SOT; lymphomas
***Cryptococcus* spp.**	HIV infection; high-dose corticosteroids (>20 mg·day^{-1} prednisone); lymphomas and chronic leukaemia; connective tissue diseases; diabetes; SOT; liver cirrhosis; sarcoidosis; TNF antagonist use

HSCT: haematopoietic stem cell transplantation; SOT: solid organ transplantation; PCP: *P. jirovecii* pneumonia.

 https://doi.org/10.1183/2312508X.10005316

treatment in patients with HIV in developed countries, *Pneumocystis jirovecii* pneumonia (PCP) and cryptococcosis are nowadays rare in this population, and are mainly diagnosed in patients following SOT or otherwise immunocompromised patients. Nevertheless, these infections still present a significant burden in HIV-infected populations in the rest of the world. Pulmonary infections caused by other yeasts and moulds such as zygomycetes, *Fusarium* and *Scedosporium* spp. are very rare, but these infections are extremely difficult to treat and associated with excessively high mortality rates of up to and over 90% [12].

The clinical appearance of pulmonary fungal infections is nonspecific and the isolated detection of fungi from respiratory samples which may commonly occur, especially in critically ill patients at the ICU, does not necessarily indicate acute infection in progress. More frequently, identification of fungal pathogens in sputum, tracheobronchial aspirates and BAL from critical ill patients only implies colonisation, especially in patients pre-treated with broad-spectrum antibiotics [13]. Nevertheless, the clinical discrimination between true infection and colonisation is the principal challenge, and remains crucial as it may lead to very different patient management and prognosis. Invasive fungal diseases are generally associated with high morbidity and mortality (up to 80%), especially if the initiation of a specific therapy is delayed [14–17]. Therefore, a high index of clinical suspicion is needed to establish the early diagnosis and treatment is often started empirically based on clinical suspicion only. However, empirical antifungal treatment may lead to over-treatment in colonised patients with the increased risk of drug-induced adverse events and higher treatment cost, but withholding or delaying antifungal therapy in true infections may have devastating consequences and increases mortality [17].

Full use of the available diagnostic essays and procedures may help to establish the early diagnosis of a pulmonary fungal infection, and to initiate a timely and targeted prescription of antifungals, which remains the key to a successful management of severe pulmonary fungal infection. Recently introduced non-culture-dependent methods such as galactomannan and 1,3-β-D-glucan essays and promising new tools such as PCR-based molecular tests may facilitate rapid and more specific diagnosis. A combination of various tests increases sensitivity, but not specificity.

The following sections provide an overview on current diagnostic approaches and therapeutic strategies for the most common pulmonary fungal infections. Noninfectious manifestations of fungal involvement in pulmonary diseases such as allergic bronchopulmonary aspergillosis in asthma sufferers and patients with cystic fibrosis (CF) as well as endemic fungal infections such as histoplasmosis, blastomycosis and coccidiomycosis are beyond the focus of this chapter.

Making the diagnosis: who to treat?

Establishing the diagnosis of pulmonary fungal infections can be challenging, mainly due to their nonspecific clinical appearance and the low sensitivity of traditional microscopic and cultural methods [7, 18, 19]. In addition, collecting proper samples for histology and culture can be difficult in neutropenic and thrombocytopenic patients, and may be a further obstacle to identifying the causative pathogen in patients with suspected pulmonary fungal diseases [18]. Therefore, a high level of awareness is needed in the management of patients at risk and early clinical suspicion of fungal infection should prompt further "aggressive" aetiological tests and evaluation. Most commonly, persisting fever in immunocompromised patients unresponsive to broad-spectrum antibiotics and radiographic findings compatible

with a fungal infection or a deterioration of pulmonary function and refractory fever in mechanically ventilated critical ill patients are considered as suspicious "early clinical signs" that should trigger assumption of a fungal aetiology [20]. In 2002, a consensus group of the European Organisation for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Disease Mycosis Study Group aimed to standardise the definition of invasive fungal disease primarily in haematological and cancer patients to foster the identification of homogeneous patient populations for clinical and epidemiological research [21]. Three degrees of reliance were defined for the diagnosis of an invasive fungal diseases based on host-specific, clinical and mycological features: "proven", "probable" and "possible" invasive fungal disease. Although originally established for research in recipients of HSCT and cancer patients only, these definition were progressively transferred into clinical practice. To overcome some limitations of the earlier definitions and to account for the introduction of new non-culture-dependent methods for the detection of fungi, a revised version of the definitions was published in 2008 (table 2). The revised definitions are now applicable to all groups of immunocompromised patients, but still do not include all patient groups at risk (*i.e.* the critically ill are still not covered) [22]. It is noteworthy that they generally do not cover PCP and should by definition only be used for research purposes. Nevertheless, the presence of invasive fungal disease is proven by histopathological, cytopathological or direct microscopic demonstration of fungal elements in biopsies of diseased tissues or recovery of moulds or yeasts from a culture of a specimen obtained by a sterile procedure from a normally sterile site in the presence of clinical or radiographic abnormalities consistent with an infectious disease process. The definitions of probable and possible invasive fungal disease may be used in clinical practice to facilitate and to guide the decision to initiate antifungal treatment, keeping in mind the afore-mentioned limitations.

The appropriate diagnostic work-up of suspected pulmonary invasive fungal disease usually involves a combination of laboratory and microbiological tests and culture, radiographic imaging, and (if possible) histological and cytological examination [23–25]. Due to the limited diagnostic value of conventional chest radiographs in patients with suspected fungal infection and the fact that abnormalities seen on a chest radiograph usually prompt a pulmonary CT scan to more specifically identify the underlying aetiology, standard chest radiography plays only a marginal role in the diagnosis of invasive fungal disease and pulmonary CT scans (preferably in high resolution) are recommended irrespective of the results of previous chest radiography [24, 26–28]. The routine use of contrast-enhanced chest CT scans is not necessary, but should be considered if a nodule or a mass is in the vicinity of large vessels [25]. The main benefits of radiographic imaging are to identify the site of infection, to evaluate the number and type of lesions, and to assess their size and distribution. Furthermore, imaging also helps guide invasive diagnostic procedures such as bronchoscopy for BAL and biopsy and transthoracic CT-guided biopsy to the most affected areas to increase their diagnostic yield. The definitive diagnosis of invasive fungal disease requires histopathological evidence of tissue invasion or a positive culture. Therefore, performance of invasive diagnostic procedures, notably bronchoscopy including BAL and CT-guided biopsy, should always be pursued whenever possible [25]. Both procedures are generally considered as safe in patients at risk for invasive fungal disease with a reasonable risk–benefit ratio [25, 29].

Sampsonas *et al.* [29] evaluated a standardised protocol for BAL in 284 consecutive patients mainly with haematological malignancies; only 10 BAL-related adverse events were observed with only one being classified as severe and none was fatal. Due to the lower diagnostic yield of BAL in patients with predominantly peripheral nodular lesions, transthoracic CT-guided needle, transbronchial and video-assisted thoracoscopic biopsy

 https://doi.org/10.1183/2312508X.10005316

Table 2. Revised 2008 definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycosis Study Group adapted to pulmonary/respiratory invasive fungal disease

Proven invasive fungal disease

One of the following criteria:

1) Histopathological, cytopathological or direct microscopic demonstration of hyphae or melanised yeast-like forms, or yeast cells in a specimen obtained by a sterile procedure from the affected site (if usually sterile) showing evidence of associated tissue damage.
2) Recovery of a mould or yeast in culture from a specimen (excluding BAL fluid, a cranial sinus cavity specimen and urine) obtained by a sterile procedure from a normally sterile site or blood from a host with an illness compatible with invasive fungal disease.
3) Detection of *Cryptococcus* antigen in cerebrospinal fluid.

Probable and possible pulmonary invasive fungal disease

Probable pulmonary/respiratory invasive fungal disease requires the presence of a host factor, a clinical criterion and a mycological criterion. At least one of the following criteria from each category has to be fulfilled. Cases that meet the criteria of a host factor and a clinical criterion, but for which mycological criteria are absent, are considered possible pulmonary invasive fungal disease.

Host factors

1) Recent history of neutropenia (<500 neutrophils·mm^{-2}) for >10 days temporally related to the onset of fungal disease.
2) Receipt of an allogeneic haematopoietic stem cell transplantation.
3) Prolonged use of corticosteroids (excluding patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg·kg^{-1}·day^{-1} of prednisone equivalent for >3 weeks.
4) Treatment with other recognised immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies or nucleoside analogues during the past 90 days.
5) Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).

Clinical criteria

Must be consistent with the mycological findings, if any, and must be temporally related to the current episode; alternative aetiology should have been excluded.

1) The presence of one of the three following signs on CT: a) dense, well-circumscribed lesions with or without a halo sign, b) air crescent sign, or c) cavity.
2) The presence of one of the following signs on bronchoscopic analysis: a) tracheobronchial ulceration, b) nodule, c) pseudomembrane, d) plaque or e) eschar.

Mycological criteria

1) Direct test (cytology, direct microscopy or culture). Mould in sputum, BAL fluid, bronchial brush or sinus aspirate samples, indicated by: a) presence of fungal elements indicating a mould and/or b) recovery by culture of a mould.
2) Indirect tests (detection of antigen or cell wall constituents, excluding PCR). One of the following: a) aspergillosis (galactomannan antigen detected in plasma, serum, BAL fluid or cerebrospinal fluid) or b) invasive fungal disease other than cryptococcosis and zygomycosis (1,3-β-D-glucan detected in serum).

Information from [22].

should be preferred in this type of presentation, although BAL may have the additional benefit to confirm or rule out other microbial pathogens. The crucial role of bronchoscopy in diagnosing pulmonary fungal infection is further supported by the possibility to directly visualise endobronchial and endotracheal lesions that might be suggestive of fungal involvement not only in severely immunosuppressed patients but also in critically ill ICU patients with little or no overt immunosuppression.

Yazicioglu Mocin *et al.* [30] demonstrated that the presence of whitish sticky secretions together with oedematous, hyperaemic and irregular mucosa accompanied by whitish mucosal plaques and subsequent nodular lesions should raise suspicion of a fungal cause. The authors were able to provide histopathological proof of fungal involvement in >50% of all cases with endobronchial and endotracheal whitish plaques, mainly *Candida* spp. and less frequently *Aspergillus* spp., compared with only 6.7% when plaques were absent. However, in clinical practice, an invasive diagnostic approach is often precluded due to the critically ill nature of the patient and significant comorbidities such as severe hypoxaemia and pancytopenia, especially when transfusion refractory thrombocytopenia is present.

Recently, non-culture-based tests for the identification of invasive fungal infections relying on detecting components of the fungal cells have been introduced to the armamentarium of diagnostic procedures in suspected fungal infections. Detection of galactomannan and 1,3-β-D-glucan in blood or BAL fluid is nowadays widely available and may facilitate early diagnosis of invasive fungal disease. Galactomannan is a molecule that is found in the cell wall of *Aspergillus* spp. hyphae and its detection in blood or BAL fluid is an accurate marker for the diagnosis of invasive (pulmonary) aspergillosis [31–36]. In high-risk patients with haematological malignancies or allogeneic HSCT, the galactomannan assay in blood has a good sensitivity of ∼71% and a specificity of almost 90% [34]. However, in other populations, especially in non-neutropenic patients, the diagnostic appropriateness appears to be considerably lower and sensitivity decreases to as low as ∼20% in SOT recipients [37–39]. Serum galactomannan is also less sensitive in patients with more indolent manifestations of pulmonary aspergillosis such as aspergilloma (38%) and patients with chronic pulmonary aspergillosis (CPA) (23%) or COPD [40–42]. Nevertheless, serum galactomannan can often be detected early (7–10 days) before the onset of clinical signs and symptoms or other diagnostic clues become apparent, and monitoring of galactomannan can potentially allow initiation of pre-emptive antifungal therapy (discussed later in this chapter) before life-threatening infection occurs [32]. However, caution should be taken in the interpretation of blood galactomannan assays in patients receiving mould-active prophylaxis as its sensitivity may be reduced and false-negative results can occur in breakthrough infections [35, 43]. Alternatively, BAL fluid can be used for galactomannan detection in pulmonary infection. Most studies addressing the value of galactomannan detection in BAL fluid have demonstrated high sensitivity for diagnosing invasive aspergillosis >70% and thus indicate a better diagnostic validity of galactomannan assays in BAL fluid compared with blood, especially in non-neutropenic patients on systemic corticosteroids and even in haematological patients receiving mould-active prophylaxis [44–48]. The currently recommended thresholds for positivity of galactomannan assays are an optical density of >0.5 in blood and >1.0 in BAL fluid.

Whereas galactomannan is quite specific for *Aspergillus* spp., the measurement of 1,3-β-D-glucan, a constituent of the cell wall of most fungi except *Cryptococcus* spp. and zygomycetes, may be considered as a "pan-fungal" assay for invasive fungal infections and is nowadays applied mainly in the diagnosis of invasive candidiasis and PCP. This test has been evaluated in high-risk haematological patients, allogeneic HSCT recipients and critically ill ICU patients with sepsis, showing high sensitivity and specificity (both >90%) for proven invasive fungal infection, without allowing the diagnosis of a specific fungal infection to be established [49–52]. Therefore, a combination of both tests may increase their diagnostic value. Galactomannan and 1,3-β-D-glucan assays may both be false positive in the context of concomitant administration of β-lactam antibiotics (*e.g.* piperacillin–tazobactam and amoxicillin–clavulanate), albumin and immunoglobulins [53, 54].

 https://doi.org/10.1183/2312508X.10005316

The use of PCR-based assays is promising. A recent Cochrane review analysed the diagnostic value of PCR in the diagnosis of invasive aspergillosis, and showed a mean sensitivity and specificity of 80.5% and 78.5% for a single positive test result, and 58.0% and 96.2% for two consecutive positive test results, respectively [55]. However, until now the widespread use of PCR has been limited mainly by a lack of standardisation and validation of the available tests. To overcome this limitation, the European *Aspergillus* PCR Initiative recently evaluated a standardised PCR, showing both appropriate sensitivity and specificity, and that the sensitivity of *Aspergillus* PCR using plasma is superior to that using serum (94.7% *versus* 68.4%) with comparable specificity (83.3% *versus* 76.2%) [56]. Thus, the evidence is growing that the diagnostic value of PCR assays in blood is at least equivalent to that of galactomannan and 1,3-β-D-glucan testing [57]. In recent trials, *Aspergillus* PCR has increasingly been applied on respiratory samples, mainly BAL fluid, showing good sensitivity of 80–100% and specificity of >80%. More importantly, latest-generation PCR assays have the additional benefit to allow rapid detection of genetic mutations encoding for resistance to antifungals such as cytochrome CYP51A gene mutations that are linked to azole resistance [58–60].

Combining various non-culture-based assays may further increase their predictive value. A recent study showed the promising diagnostic potential for the combination of galactomannan and PCR assays from BAL fluid for diagnosing invasive aspergillosis with a sensitivity of 85% and a specificity of 97% in haematological patients [61]. In addition, this trial underlined the value of BAL fluid as a specimen for non-culture-based assays, showing superior diagnostic performance for galactomannan and PCR when BAL fluid was used compared with blood samples alone.

Thus, establishing the diagnosis of a pulmonary fungal infection remains challenging and requires a high level of awareness. The indication to start antifungal treatment in patients at risk is based mainly on a balanced consideration of host factors, clinical signs and symptoms, which are usually nonspecific, findings of imaging, microbiological cultures and non-culture based assays, and histological and cytological results. Due to the low overall diagnostic yield of conventional microbiological culture, the role of non-culture-based diagnostic tests (galactomannan, 1,3-β-D-glucan and PCR) from blood, BAL fluid and other respiratory secretions is progressively gaining importance in clinical practice and may facilitate the definitive diagnosis of pulmonary fungal infections. However, the results always need to be interpreted with caution and in the context of clinical and radiographic findings, because they may be irrelevant as fungal colonisation as well as false-positive results may occur. So far, the histopathological, cytopathological or direct microscopic demonstration of fungal elements with signs of tissue invasion in samples obtained by a sterile procedure and recovery of moulds or yeasts by culture from these specimens or blood in the context of a clinically overt infectious disease remains the gold standard to prove the presence of an invasive pulmonary fungal infection.

Treating pulmonary fungal infections: when to treat?

Fungi are highly developed eukaryotic organisms that possess cells with nuclei and organelles, and have genetic similarities to human cells. Thus, the structural and functional differences between eukaryotic fungal cells and human cells are only small, limiting the number of potential and selective targets for antifungal drugs. Subsequently, antifungal

drugs bear a higher risk for direct interaction with human host cells and impairment of their structures and functions. Thus, drug-induced side-effects can occur more frequently compared with antibiotic therapy targeted against bacterial infections.

Most antifungal agents for systemic treatment come from three major classes of drugs: azoles, polyenes and echinocandins. Azoles can be further classified into two groups: triazoles (fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole) and imidazoles (ketoconazole). Azoles inhibit the conversion of lanosterol to ergosterol (*i.e.* the main sterol in the fungal cell membrane). Depletion of ergosterol damages the cell membrane and results in inhibition of fungal growth and cell death. Polyenes (*e.g.* amphotericin B, nystatin and pimaricin) interact with ergosterol to form channels through the fungal cell membrane, causing the cells to become leaky and resulting in cell death. Echinocandins (anidulafungin, caspofungin and micafungin) are a relatively new class of antifungal that act by inhibiting the synthesis of 1,3-β-D-glucan in the cell wall.

The key to successful management of pulmonary fungal infections is timely initiation of antifungal treatment in high-risk patients with pulmonary fungal infection as a delay in treatment negatively affects outcome and increases mortality. Therefore, antifungals are not only indicated in proven invasive fungal infections, but should also be prescribed in patients at high risk to prevent infection or in patients with strongly suspected pulmonary fungal infection. Initiation of antifungal treatment should never be delayed until the results of all diagnostic tests are available, even if pulmonary fungal infection is only suspected clinically. As a result, various treatment strategies have been implemented in clinical routine and prescription of antifungals can be divided into prophylactic, empiric, pre-emptive and definitive (table 3).

In general, prophylactic treatment refers to the preventive administration of an antifungal agent to patients at highest risk of invasive fungal infection without any overt signs and symptoms relatable to an infection in progress. This strategy is well established in haematological and cancer patients with prolonged neutropenia, and recipients of HSCT and SOT (most notably following lung transplantation) [25, 62–64]. However, the evidence for widespread antifungal prophylaxis in critically ill ICU patients is weak and it is therefore not generally recommended [65]. Evidence-based recommendations for

Table 3. Treatment strategies

Prophylactic treatment	Administration of antifungals in high-risk patients, notably with prolonged neutropenia, without clinical evidence of an acute infection to prevent fungal infection
Empiric treatment	Initiation or modification of antifungal therapy in patients at risk with neutropenia and continuing fever for 4–7 days without a known source and despite appropriate antibacterial therapy
Pre-emptive treatment	Antifungal treatment in patients with acute pulmonary infection and high suspicion of fungal aetiology based on non-culture-based assays or imaging highly suggestive of pulmonary fungal infection without definitive proof by microscopy or culture
Definitive treatment	Targeted antifungal treatment in patients with proven fungal aetiology or probable fungal infection according to European Organisation for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Disease Mycosis Study Group criteria (table 2)

 https://doi.org/10.1183/2312508X.10005316

prophylactic antifungal therapy in various patient populations targeting the most common pulmonary fungal pathogens are given in table 4.

Empiric treatment is specified as the prescription of antifungal treatment to patients at high risk of invasive fungal disease, and with established clinical signs and symptoms, but without any microbiological documentation. As a result, the empiric treatment approach may lead to overexposure to antifungals due to the poor specificity of clinical signs (*e.g.* persisting febrile neutropenia) and radiographic findings. Accordingly, the inclusion of non-culture-based assays into the decision-making process to initiate antifungal treatment may increase diagnostic and therapeutic accuracy, and also allows us to detect incipient pulmonary fungal infections in high-risk patients even before the onset of clinical symptoms. This treatment approach is known as pre-emptive or biomarker-driven antifungal treatment and administration of antifungals is based on positive findings of early diagnostic tests such as non-culture-based assays (galactomannan, 1,3-β-D-glucan and fungal PCR) or imaging (thoracic CT scans) highly suggestive of pulmonary fungal infection in an appropriate clinical context. Subsequent prospective RCTs comparing empiric and pre-emptive treatment strategies, mainly in haematological and cancer patients with high-risk neutropenia, have confirmed that a pre-emptive approach significantly reduces antifungal exposure (up to 78%) compared with empiric antifungal therapy without compromising survival. Additionally, in patients with pre-emptive treatment an increase was observed in definitively identified and successfully managed proven and probable invasive fungal disease, mainly due to their earlier detection [69–73].

Finally, definitive or targeted therapy requires a precise fungal pathogen identification to be defined. Both empiric and pre-emptive therapy should always be adapted, de-escalated or terminated ("antibiotic stewardship") whenever the definite results of all diagnostic and microbiological tests are available.

Table 4. Prophylactic regimens with high-grade recommendations for invasive aspergillosis and *Pneumocystis jirovecii* pneumonia (PCP)

Risk groups	Invasive aspergillosis	PCP
Allogeneic haematopoietic stem cell transplantation		
Initial neutropenic phase		TMP-SMX
Graft-*versus*-host disease phase (start at 90–100 days)	Posaconazole	TMP-SMX
Acute myeloid leukaemia (remission-induction chemotherapy)	Posaconazole	
Acute lymphoblastic leukaemia		TMP-SMX
HIV ($CD4^+$ count <200 cells·μL^{-1} or <14%)		TMP-SMX
Solid organ transplantation	No definitive recommendations except for lung transplantation: itraconazole; voriconazole; aerosolised formulations of amphotericin B	TMP-SMX

No definitive recommendations exist for cryptococcosis. TMP-SMX: trimethoprim–sulfamethoxazole. Information from [25, 63, 66–68].

Specific pulmonary fungal infections: how to treat?

Pulmonary manifestations of *Aspergillus* infection

Aspergillus spp. is ubiquitous in the environment, and may produce spores that can easily be inhaled and then penetrate the alveoli. Inhalation of conidia into the lungs is thus considered the usual route of human infections. Accordingly, *Aspergillus* spp. is one of the most frequently detected fungal pathogens in pulmonary infections, particularly in immunocompromised patients, accounting for >85% of all invasive mould infections in humans. The majority of all cases of aspergillosis (up to 90%) are caused by *Aspergillus fumigatus* [6, 11, 74]. Other less common species that have been detected in the context of pulmonary and invasive aspergillosis include *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus terreus*.

After inhalation of *Aspergillus* conidia, a wide range of pulmonary and systemic clinical syndromes can be observed, and the severity of the disease mainly depends on the host's immune status. Although inhaled conidia are rapidly and sufficiently eradicated in immunocompetent individuals, impairment of phagocytosis and reduced macrophage activity allows persistence of spores in the alveoli and airways. Prolonged neutropenia and deficient T-lymphocyte responses then additionally favour progression of infection and tissue invasion by hyphae [3, 5]. Thus, effective antifungal immunity depends on an efficient interaction between different parts of the innate and acquired immunity, including pattern recognition receptors, such as Toll-like receptors (TLRs), C-type lectins, mannose binding lectin 2 and long pentraxin 3 (PTX3), neutrophils, natural killer cells, dendritic cells, macrophages, and T-cells [75–94].

The spectrum of *Aspergillus*-associated diseases ranges from acute invasive pulmonary aspergillosis (IPA) primarily affecting profoundly immunocompromised patients to CPA mainly in those with underlying pulmonary diseases and *Aspergillus* tracheobronchitis in patients with CF and lung transplant recipients [95–98]. Finally, a fungal sensitisation may result in allergic bronchopulmonary aspergillosis in severe asthma sufferers and patients with CF. The different clinical manifestations of pulmonary aspergillosis can be regarded as a continuum of diseases, each characterised by the degree of immunological compromise of the host, and one entity may evolve into another depending on the host's immune status [95].

IPA is a life-threatening disease distinguished by high mortality rates of up to 90% among patients with severe immunological impairment and dissemination to other organs may develop, although often underdiagnosed [99, 100]. The clinical occurrence is characterised by an acute onset of symptoms and rapid progression within days to weeks. However, clinical symptoms are nonspecific, frequently including fever (that may be absent in non-neutropenic patients), cough, and, as signs of pulmonary infarction caused by angioinvasion and vascular occlusion, chest pain and haemoptysis [99]. Radiographic signs are also nonspecific, ranging from single or multiple nodular lesions to larger masses and diffuse bilateral infiltrates as well as cavitations. Nevertheless, chest CT scans can provide first hints of IPA if sharply demarcated nodules with surrounding ground-glass opacity ("halo sign") or cavitated lesions with an intracavitary mass ("air crescent sign") are observed that are both often associated with IPA in neutropenic patients, even though nonspecific, either in early stages (halo sign) or later on after neutrophil recovery (air crescent sign). In non-neutropenic IPA patients, angioinvasion is often lacking, and the

 https://doi.org/10.1183/2312508X.10005316

clinical course may be more protracted with clinical symptoms and radiographic signs developing over weeks rather than days.

Prolonged neutropenia is still the leading risk factors for IPA despite the introduction of posaconazole prophylaxis in neutropenic high-risk haematological patients in 2007. Nevertheless, after implementing posaconazole prophylaxis, a significant reduction in IPA was observed in patients with acute haematological malignancies and HSCT recipients, and a shift towards non-*Aspergillus* mould infections was seen in two studies from France and Austria [66, 67, 101, 102]. Other populations at higher risk for IPA include recipients of SOT (especially following lung or heart transplantation) and non-neutropenic patients, such as critically ill patients at the ICU, patients with severe COPD or liver disease and, in general, patients receiving immunosuppressive medication or long-term corticosteroids (also see table 1) [99, 103, 104].

Furthermore, recent research has highlighted the importance of genetic variations and polymorphisms as individual risk factors for increased susceptibility to invasive fungal infections in populations at risk. As is known from clinical practice, not all patients presenting with typical risk factors such as chemotherapy, immunosuppressive treatment and SOT or HSCT actually develop pulmonary fungal infection, despite comparable levels of immunosuppression. Whereas some patients apparently seem to be protected from pulmonary fungal infections, others will rapidly develop severe and invasive pulmonary fungal infections. Recently, it has become clear that this observation could at least in part be explained by genetic variations and polymorphisms of the host (and/or donor of HSCT) that may increase or decrease susceptibility to fungal infections [93, 94, 105]. Many different genetic targets have been studied, and the most frequently investigated genes include those encoding for pattern recognition receptors (mainly TLRs, Dectin-1 and PTX3), cytokines and chemokines, and their receptors [106–114]. Most studies confirmed an association between the presence of specific polymorphisms in various genes and susceptibility to invasive fungal diseases. However, some of the results were conflicting, lacked reproducibility and the identified polymorphisms were infrequent in the respective population at risk. So far, the most promising results have been reported for frequent polymorphisms in the *PTX3* gene, such as 281A/G and 735A/C [113, 114].

Nevertheless, our growing understanding of genetic diversity and its impact on susceptibility to fungal infections, and the increasing availability and accessibility of techniques such as high-throughput single nucleotide polymorphism genotyping and genome-wide association studies, will potentially allow us in the near future to identify and stratify patients at risk according to their individual genetic make-up and associated susceptibility to fungal infection. This will then open the door to precision medicine and tailored regimens for treatment and prophylaxis of invasive fungal diseases, which is of great importance when facing the high costs of conventional prophylactic and therapeutic strategies, potential drug interactions, toxicity, and emergence of resistant strains and breakthrough infections.

A less frequently appreciated risk factor for invasive aspergillosis represents preceding or concurrent viral respiratory infection (H1N1 influenza, adenovirus and cytomegalovirus) as it may be associated with profound immunosuppressive effects, particularly in lung transplant patients [115].

Treatment should be started as early as possible in all patients with strongly suspected IPA, with diagnostic procedures performed in parallel (empiric and pre-emptive strategy).

Antifungals from all three classes may be used to treat IPA (table 5). However, voriconazole is considered the drug of first choice based on available evidence and current guideline recommendations [25].

In the first randomised trial comparing voriconazole with amphotericin B deoxycholate as primary treatment of IPA published in 2002, voriconazole demonstrated significantly higher cure rates (53% *versus* 32%) and improved survival (71% *versus* 58%) [119]. Since then, multiple subsequent studies have confirmed the superiority of voriconazole and consolidated its role as the first-line drug in IPA. In severely affected patients, treatment should always be started parenterally and may be switched to oral administration after a favourable initial response; less severe cases may be treated orally from the beginning. Therapeutic drug monitoring is advisable during oral treatment to ensure that dosing is adapted to achieve maximised target serum levels and to minimise toxicity. The use of voriconazole can be limited and complicated by extensive drug–drug interaction (voriconazole is both a substrate and an inhibitor of cytochromes CYP2C19 and CYP3A), emergence of resistance (the prevalence of azole resistance in *A. fumigatus* worldwide is ~3%) and drug toxicity, particularly hepatotoxicity [120–123]. Whenever voriconazole is started empirically in suspected pulmonary fungal infection it is important to keep in mind that most fungi causing mucormycosis are inherently resistant to the most widely used antifungals, including voriconazole.

Alternative treatment options (table 5) include novel triazoles such as isavuconazole and polyenes, notably liposomal amphotericin B (although note *A. terreus* is inherently resistant to amphotericin B) [25, 99]. The recently published SECURE (Isavuconazole *versus* voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi) trial demonstrated noninferiority of isavuconazole for IPA treatment compared with voriconazole and the potential benefit of a more favourable toxicity profile [124]. Echinocandins are not recommended as first-line monotherapy, but recent trials suggest a potential benefit and decrease in mortality when echinocandins are administered in combination with voriconazole compared with voriconazole monotherapy [125–128]. However, empiric combination therapy should mainly be considered in regions with locally high rates of azole resistance in the environment.

In cases of refractory or progressive IPA despite treatment, an individualised strategy is recommended, and may include changing the antifungal class, adding an agent from another antifungal class, tapering or treating underlying immunosuppression if possible and, finally, resection of necrotic areas when feasible in selected patients [25].

Although the optimal duration of IPA treatment has not yet been well defined, current guidelines recommend to continue treatment for at least a minimum of 6–12 weeks depending on the clinical response and individual factors, mainly the degree and duration of immunosuppression. Therapy should ideally be continued until complete resolution of all clinical sign and symptoms and radiographic findings [25]. In a recently published survey of the Transplant Associated Infection Surveillance Network, the mean duration of IPA treatment in SOT patients was 115 days [129].

Less severe forms of aspergillosis such as subacute invasive aspergillosis (formerly named chronic necrotising pulmonary aspergillosis), chronic cavitary pulmonary aspergillosis (CCPA), simple aspergilloma and *Aspergillus* nodules are summarised as CPA [116]. Although these entities are not precisely defined and overlap may occur in clinical and

 https://doi.org/10.1183/2312508X.10005316

Table 5. Specific treatment recommendations for the most common pulmonary fungal infections: pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia and pulmonary cryptococcosis

Pathogen	First-line therapy	Alternative regimens
***Aspergillus* spp.**		
Invasive pulmonary aspergillosis	Voriconazole (loading dose 6 mg·kg^{-1} *i.v.* twice daily for 1 day, followed by 4 mg·kg^{-1} *i.v.* twice daily or *p.o.* dosage 200–300 mg twice daily) for 6–12 weeks; adjust *p.o.* voriconazole treatment with therapeutic drug monitoring (goal trough day 4: 1.0–5.5 mg·L^{-1})	Isavuconazole (200 mg *i.v.* three times daily on day 1 and day 2, followed by 200 mg *i.v.* or *p.o.* once daily) OR liposomal amphotericin B$^{\#}$ (3 mg·kg^{-1}·day^{-1} *i.v.* for 6–12 weeks)
	Salvage therapy: caspofungin (70 mg *i.v.* day 1; thereafter 50 mg·day^{-1} *i.v.*); micafungin (100–150 mg·day^{-1} *i.v.*); posaconazole (200 mg four times daily)	
	Recurrence prophylaxis is recommended following successful treatment, when subsequent immunosuppression is required/present	
Chronic pulmonary aspergillosis		
Subacute invasive pulmonary aspergillosis	Treat as described for invasive pulmonary aspergillosis	
Chronic cavitary pulmonary aspergillosis	Itraconazole (200 mg *p.o.* twice daily; adjust with therapeutic drug monitoring) OR voriconazole (150–300 mg *p.o.* twice daily; adjust with therapeutic drug monitoring) for a minimum of 6–9 months; in severe or progressive disease consider *i.v.* treatment (voriconazole or liposomal amphotericin B as described for invasive pulmonary aspergillosis)	Posaconazole (400 mg *p.o.* twice daily (liquid) or 300 mg *p.o.* once daily (tablets))
Simple aspergilloma	No indication for antifungal therapy	
Pneumocystis jirovecii	Trimethoprim–sulfamethoxazole (15 mg trimethoprim component·kg^{-1}·day^{-1} *p.o.* or *i.v.*) divided into three or four doses for a minimum of 14 days (HIV-negative) or 21 days (HIV-positive)	Primaquine+clindamycin (30 mg *p.o.* once daily +600 mg *i.v.* three times daily) OR pentamidin (4 mg·kg^{-1} *i.v.* or aerosol); atovaquone (only for mild cases) (750 mg *p.o.* three times daily)
	Recurrence prophylaxis is recommended following successful treatment, when subsequent immunosuppression is required/present	

Continued

Table 5. Continued

Pathogen	First-line therapy	Alternative regimens
***Cryptococcus* spp.**		
Mild to moderate symptoms and focal pulmonary infiltrates Severe and/or disseminated pulmonary cryptococcosis	Fluconazole (400 mg *p.o.* or *i.v.* once daily) for a minimum of 6–12 months Induction: amphotericin B deoxycholate (0.7–1.0 $mg \cdot kg^{-1} \cdot day^{-1}$ *i.v.*) or liposomal amphotericin B (3–4 $mg \cdot kg^{-1} \cdot day^{-1}$ *i.v.*) AND flucytosine (100 $mg \cdot kg^{-1} \cdot day^{-1}$ *p.o.* divided into four doses) for at least 2–4 weeks Consolidation: fluconazole (400–800 mg *p.o.* once daily) for a minimum of 8 weeks Maintenance: fluconazole (200–400 mg *p.o.* once daily) for 6–12 months (HIV patients at least 12 months; discontinuation only when $CD4^+$ count >100 $cells \cdot \mu L^{-1}$)	

#: *Aspergillus terreus* is inherently resistant to amphotericin B. Information from [25, 116–118].

https://doi.org/10.1183/2312508X.10005316

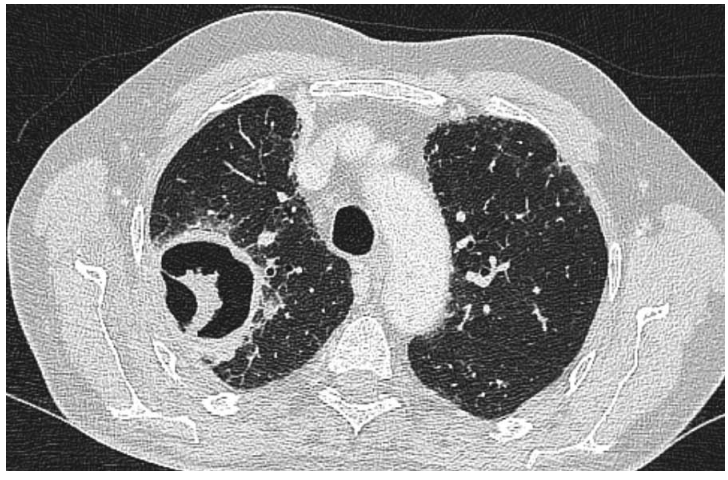

Figure 1. Chest CT scan of a 67-year-old male patient with COPD and long-term corticosteroid use for chronic rheumatic arthritis showing a large cavitation containing a fungal ball and surrounding infiltrate. Together with positive *Aspergillus* serology, this finding is compatible with chronic cavitary pulmonary aspergillosis.

imaging features, they all have in common that hyphal vascular invasion is usually not present, but may be observed in subacute IPA [130]. The heterogeneous group of CPA mainly affects patients with underlying pulmonary comorbidity and no or only mild to moderate immunological compromise. Most typically, CPA is found in patients with COPD, sequelae following TB, NTM infections, bronchiectasis, diabetes mellitus, malnutrition, alcoholism, and prolonged administration of corticosteroids and other moderate immunocompromising agents [96–98].

Patients typically present with weight loss, cough that is often accompanied by haemoptysis, fatigue and chest pain. Symptoms mainly develop over weeks to months, usually >3 months. However, in subacute IPA, the clinical progression is commonly more rapid (<3 months) compared with other forms of CPA. The distinct radiographic pattern of CPA includes the formation and enlargement of a single or multiple cavities over at least 3 months with or without an incorporated fungal ball or irregular intraluminal material (CCPA; see figure 1), and in subacute IPA a mixed picture with cavitation, nodules and progressive consolidations with possible cavitation [116]. The diagnosis of CPA is usually based on an appropriate clinical and radiographic appearance accompanied by positive *Aspergillus* serology (*Aspergillus*-specific IgG and, less reliably, precipitins) or microbiological evidence (*Aspergillus* growth in culture, strongly positive *Aspergillus* antigen or PCR from respiratory fluids; in subacute IPA, additionally, biopsies showing hyphae on microscopy with invasion of the lung parenchyma) [116, 131, 132]. Whereas sensitivity of galactomannan testing in serum is very low in most forms of CPA (only 23% in a recent study), except for subacute IPA, galactomannan antigen detection from BAL provides good sensitivity (77.2–85.7%) and specificity (~77%) [41, 133, 134]. The diagnosis of a simple aspergilloma only requires documentation of a single cavity containing a fungal ball in combination with serological or microbiological verification of *Aspergillus* spp. [116].

As evidence is scarce, the decision to initiate antifungal treatment in patients with CPA should be based on the type of CPA, clinical signs and symptoms, and eligibility for surgery. However, oral therapy with triazoles has been shown to stabilise and improve clinical

symptoms and radiographic findings with acceptable tolerability in CCPA [135–138]. Furthermore, treatment can be effective in the prevention and treatment of potentially life-threatening haemoptysis. Therefore, oral triazole treatment (itraconazole, voriconazole and posaconazole) may be considered in symptomatic patients with only minor symptoms and localised radiographic findings [116]. In patients with progressive CCPA or failure of oral triazole treatment, and in patients with initially severe CCPA, intravenous (*i.v.*) administration of antifungals should be considered, ideally as induction therapy followed by oral maintenance therapy. Voriconazole as well as liposomal amphotericin B and some of the echinocandins (*i.e.* micafungin and caspofungin) have been demonstrated to be effective therapeutic options [139, 140]. Treatment should be continued for at least 4–6 months as response to therapy is usually slow. In some case a prolonged treatment of up to 9 months might be necessary to observe improvement. As relapses occur frequently, long-term suppressive treatment should be considered in responders. For localised cavitary lesions and simple aspergilloma, surgical resection can be an option, particularly to control severe and recurrent haemoptysis. Antifungals are generally not indicated in simple aspergilloma as no beneficial treatment effects have been observed. Patients with subacute IPA should be treated as patients with IPA (as discussed earlier).

An important differential diagnosis to invasive forms of pulmonary aspergillosis is mucormycosis, a rare but life-threatening fungal infection caused by members of the order *Mucorales*, formerly known as zygomycetes [141]. Although mucormycosis is a rare pulmonary fungal infection, its frequency is currently on the increase, and it is associated with high mortality rates of 37–100% in cases with pulmonary involvement depending on underlying risk factors, dissemination, species and treatment [142–147]. Mucormycosis shares close clinical and radiological features with invasive aspergillosis, but some signs and symptoms may denote infection caused by *Mucorales*. Of specific importance is the fact that *Mucorales* are resistant to voriconazole, which is the first-line treatment of IPA, and to echinocandins. Therefore, breakthrough infections in patients on voriconazole treatment should always raise the suspicion of mucormycosis. Furthermore, galactomannan and 1,3-β-D-glucan are not components of the cell walls of *Mucorales*, and hence galactomannan and 1,3-β-D-glucan assays are always negative in patients with mucormycosis. Thus, negative results of both assays in blood and BAL fluid from patients with high clinical and radiographic suspicion of invasive pulmonary fungal infection should direct the attention towards mucormycosis. Concomitant involvement of the sinus is more frequent in patients with pulmonary mucormycosis compared with patients with pulmonary aspergillosis. Accordingly, sinusitis may be an additional clue to start thinking about mucormycosis in patients with suspected pulmonary infection [147, 148]. Although the radiographic features of mucormycosis are nonspecific, the presence of the reversed halo sign, *i.e.* a focal ground-glass opacity with surrounding ring- or crescent-shaped consolidation, may be indicative of mucormycosis, although not pathognomonic. In addition to typical risk factors for invasive pulmonary fungal infection (*e.g.* chemotherapy, immunosuppressive therapy, HSCT and SOT), diabetes mellitus is more frequently described as an underlying disease in patients with mucormycosis, especially if poorly controlled.

The mainstay to establish the definitive diagnosis of pulmonary mucormycosis remains the proof of *Mucorales* in culture and/or histopathology from samples of involved tissues. Direct microscopic examination and *Mucorales*-specific PCR assays may facilitate the diagnostic approach. Treatment of choice for mucormycosis is liposomal amphotericin and alternatively posaconazole or other forms of lipid-associated formulations of amphotericin. Surgical debridement should always be considered, if possible [149].

 https://doi.org/10.1183/2312508X.10005316

P. jirovecii pneumonia

P. jirovecii has a substantial impact on morbidity and mortality in immunocompromised populations. Due to its ubiquitous presence in the environment, a high prevalence of positive serology can be found in the general population, as an indicator of previous contact with this pathogen [150]. Therefore, it is currently under debate whether the clinical manifestation of PCP is either the result of reactivation of a latent infection or recent re-infection, both in the presence of immune compromise [151, 152]. For a long time PCP used to be one of the typical opportunistic indicator infections in HIV-positive individuals, but with the introduction of highly active antiretroviral therapy (HAART) and routine use of PCP prophylaxis in patients with a low $CD4^+$ lymphocyte count (<200 cells·μL^{-1}) the incidence of PCP has significantly decreased in developed countries. Nowadays, further risk groups have become the focus of interest, such as haematological and cancer patients, recipients of SOT and HSCT, and, in general, patients receiving immunosuppressive agents (*e.g.* for rheumatological diseases) [143].

As in other pulmonary fungal infections, the clinical appearance of PCP is nonspecific; patients usually present with fever, dry cough and shortness of breath that can rapidly progress to severe hypoxaemia and respiratory failure. The clinical course may vary among different populations at risk. In HIV-positive patients, progression of symptoms is normally subtle and prolonged, evolving slowly over weeks, whereas non-HIV patients often witness a fulminant development of the disease within a few days [153, 154]. The first suspicion of PCP often arises from chest radiographs or, preferably, high-resolution thoracic CT scans showing bilateral perihilar interstitial infiltrates and additional cystic lesions (mainly in HIV-positive patients) in an appropriate clinical context. Confirmation of PCP is then obtained by the direct detection of the fungal organisms in BAL fluid or induced sputum with the aid of fluorescence microscopy. Recently, real-time PCR in respiratory samples has been introduced as an adjunct diagnostic tool showing good sensitivity (98–100%) and specificity (94.4–96%) [155–157]. Generally, the diagnostic yield of respiratory specimens is greater in HIV-positives compared with all other populations at risk [158]. If diagnostic bronchoscopy is not tolerated, detection of serum 1,3-β-D-glucan has been shown to augment PCP diagnosis with a high sensitivity (94.8%) and specificity (86.3%).

PCP-associated mortality is high, although it differs among non-HIV patients and the HIV-positive population (30–60% *versus* 10–20%, respectively), and deferral of treatment initiation has been identified as a major driver of mortality [143, 159, 160]. Therefore, *Pneumocystis*-targeted treatment should be started as soon as PCP is clinically and radiographically suspected. Bronchoscopy can be performed after onset of specific treatment without compromise in diagnostic yield as *Pneumocystis* remains detectable for at least up to 72 h despite therapy initiation [161]. As *Pneumocystis* is extremely resistant to traditional antifungal agents, including both polyenes and azole agents (due to lack of ergosterol in plasma membranes), high-dose trimethoprim–sulfamethoxazole is considered as the drug of first choice [162, 163]. Alternative regimens include clindamycin plus primaquine, atovaquone, pentamidine and trimethoprim–dapsone (table 5) [164]. An oral treatment strategy is feasible in patients with only mild PCP if enteral resorption is not impaired. Moderate to severe cases usually require parenteral treatment; a switch to oral sequence therapy should follow once the patient responds to therapy and has improved. PCP-specific therapy is usually continued for 14 days in HIV-negative patients, whereas HIV-positive patients usually receive a 3-week course. Prophylactic treatment is recommended in HIV-positive patients with a $CD4^+$ count <200 cells·μL^{-1} and in

HIV-negative patients receiving prolonged (>8 weeks) high-dose corticosteroids (>20 mg·day^{-1} prednisone equivalent) or other immunosuppressive treatment. In HIV-positive patients with severe hypoxaemia at initial presentation, adjuvant treatment with corticosteroids has been demonstrated to improve survival and is thus recommended. Data in non-HIV patients are conflicting and a general recommendation for the use of corticosteroids in all hypoxaemic PCP patients cannot be given [117].

Pulmonary cryptococcosis

As in most pulmonary fungal infections, inhalation of *Cryptococcus* spp., an encapsulated yeast-like fungus that is ubiquitous in the environment, is the most common route of acquisition. In healthy individuals, alveolar macrophages and CD4$^+$ T-lymphocytes constitute the first and most important line of defence against cryptococcal infections. Following inhalation of cryptococcal yeasts, oligosymptomatic and clinically nonovert infection is frequent early in life, possibly causing life-long latent infection. In a study from the USA, seropositivity for *Cryptococcus neoformans* was high (70%) among children aged ⩾5 years [165, 166]. Therefore, a change in immunological status later in life can clear the way for reactivation of a latent infection, which is considered to be the most common cause of pulmonary cryptococcosis, although re-infection may also occur [166, 167]. Accordingly, immunocompromised patients are at highest risk for developing cryptococcal infection (table 1). Worldwide, HIV remains the major underlying disease in cryptococcosis, although the availability of HAART has significantly decreased HIV-associated cryptococcal infections in developed countries, especially cryptococcal meningoencephalitis [168, 169]. However, cryptococcosis, particularly diseases caused by *Cryptococcus gatti*, is also seen in immunocompetent patients, although rarely [170, 171].

Out of the more than 70 known species within the genus *Cryptococcus*, two main species account for the majority (>90%) of human infections: *C. neoformans* and *C. gatti*. Both can cause localised pulmonary infections, but dissemination to the central nervous system (CNS), bones and skin is frequent. Therefore, cryptococcal meningoencephalitis is clinically the most common and most severe manifestation, followed by localised pulmonary infection.

The clinical picture of pulmonary involvement is variable, symptoms are nonspecific and even asymptomatic courses may occur. Whereas severe pneumonia and rapidly progressing respiratory failure were previously not uncommon in untreated HIV patients, the majority of patients with pulmonary cryptococcosis nowadays present with fever, cough, chest pain and malaise [172, 173]. Whenever headache, nausea, vomiting and visual disturbances are reported additionally at presentation, cryptococcal meningoencephalitis should be suspected and searched for. Nevertheless, lumbar puncture is recommended in all immunosuppressed patients with proven pulmonary cryptococcosis to rule out CNS dissemination as it requires more aggressive treatment to reduce mortality [174]. Radiographic imaging most frequently shows peripherally located single or multiple nodular lesions and masses, and may mimic other pathologies such as lung cancer [175–177]. The key to diagnosis remains a positive fungal culture, ideally supported by histological proof of tissue invasion, which requires invasive procedures such as bronchoscopy with BAL and transbronchial biopsies, or percutaneous, thoracoscopic or open surgery biopsy. Sputum may also be used, although the diagnostic yield is usually low [173]. In addition to culture and histology, detection of cryptococcal antigen in serum may augment diagnosis of pulmonary cryptococcosis. However, serum antigen titres in patients

 https://doi.org/10.1183/2312508X.10005316

with isolated pulmonary cryptococcosis are usually lower compared with disseminated cases, especially with involvement of the CNS [175]. In one study, relevant serum antigen titres (⩾1:64) were documented only in 22% of patients with isolated pulmonary cryptococcosis in contrast to 71% in disseminated disease [178]; in cryptococcal meningoencephalitis antigen detection has a high sensitivity and specificity (>90%) in both serum and liquor [179].

As prospective RCTs are lacking for pulmonary cryptococcosis, treatment recommendations are mainly inferred from retrospective case series, expert opinion and studies of cryptococcal meningoencephalitis in HIV-positive patients. For mild disease with only localised pulmonary infiltrates, oral treatment with fluconazole applied for 6–12 months is usually recommended. More severe cases should be treated according to cryptococcal meningoencephalitis guidelines, especially when dissemination is present; an *i.v.* induction therapy with a combination of amphotericin B deoxycholate or liposomal amphotericin B and flucytosine (5-fluorocytosine) given for 2–4 weeks is then followed by 8–10 weeks of high-dose fluconazole as consolidation therapy and finally maintenance therapy with fluconazole for up to 12 months (table 5) [118, 174, 180].

Conclusions

Detection and treatment of pulmonary fungal infections requires a high level of alertness and suspicion in patients at risk. Invasive diagnostic procedure to obtain specimens from the suspected site of infection, particularly bronchoscopy including BAL and biopsy, should always be performed whenever possible. Modern non-culture-based assays complete the diagnostic armamentarium and may potentially allow early identification of clinically relevant resistance (*e.g.* PCR) in some cases. Thus, comprehensive use of the available diagnostic essays and procedures may help to establish the early diagnosis of a pulmonary fungal infection and to initiate timely targeted prescription of antifungals, which remains the key to successful management of severe pulmonary fungal infection. Diagnostic procedures should never delay treatment initiation in patients with high suspicion of pulmonary fungal infection.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10005316

Long-term oral antibiotic treatment: why, what, when and to whom?

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Antibiotics are typically prescribed as short courses for acute infections, in order to reduce bacterial load, shift the balance in favour of host defences and thus help to overcome infection. Over the past decade, however, interest in the long-term anti-inflammatory and immunomodulatory effects of selected antibiotics has been on the increase. Since the clinical effectiveness of erythromycin was reported in diffuse panbronchiolitis in the 1980s, the use of macrolides has been adopted into many other chronic inflammatory airway diseases characterised by frequent exacerbations, including cystic fibrosis (CF), non-CF bronchiectasis, COPD, severe noneosinophilic asthma, bronchiolitis obliterans after lung transplantation and organising pneumonia. In this chapter, we discuss the indications and limitations of long-term macrolide treatment in these chronic respiratory conditions.

Cite as: Van Braeckel E, van der Eerden MM. Long-term oral antibiotic treatment: why, what, when and to whom? *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 185–205 [https://doi.org/10.1183/2312508X.10005416].

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Long-term oral antibiotic treatment: why?

Airway disorders such as COPD, cystic fibrosis (CF) and bronchiectasis, in which chronic airway inflammation and (infectious) exacerbations occur, typically result in progressive lung function decline, decreased health-related quality of life and increased risk of mortality [1–5]. The pathophysiological processes typical of these chronic inflammatory lung diseases are characterised by a vicious circle hypothesis, in which exacerbations result in increased airway inflammation, more damage to airways and therefore a higher risk for new

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exacerbations, which will finally result in progression of disease (figure 1) [4, 6, 7]. To inhibit further disease progression, interventions have to be performed directed at one of these steps of the vicious circle. Among these interventions is the implementation of long-term oral antibiotic treatment. The most widely studied class of antibiotics used for oral maintenance therapy is the macrolide group.

Long-term oral antibiotic treatment: what?

Choice of agent

Although other antibiotics, such as the tetracycline doxycycline and the fluoroquinolone moxifloxacin, have also been assigned immunomodulatory properties [8, 9], only the use of macrolides has been well documented in RCTs. Their effects in chronic inflammatory lung diseases were first studied in patients with diffuse panbronchiolitis in the 1980s [10]. Since then macrolides have been studied extensively in CF [11–14], non-CF bronchiectasis [15–17], and recently also in patients with COPD [18–20] and severe asthma [21, 22].

Structure and mechanisms of actions of macrolides

The family of macrolide antibiotics is structurally characterised by a lactone ring containing at least 12 members, with erythromycin, clarithromycin and roxithromycin containing a 14-membered lactone ring, and azithromycin (also called an azalide) containing a 15-membered lactone ring with a tertiary amino group [23, 24]. The neomacrolides azithromycin, clarithromycin and roxithromycin have excellent bioavailability with superior oral absorption and better tissue penetration than erythromycin, accumulating preferentially in (alveolar) macrophages, with azithromycin having the longest serum half-life, making it suitable for once-daily or even intermittent dosing [25–27]. Due to toxicity concerns and scarceness of data on immunomodulatory effects, the ketolide telithromycin is less convenient for long-term use and will therefore not be discussed further in this chapter [28–30].

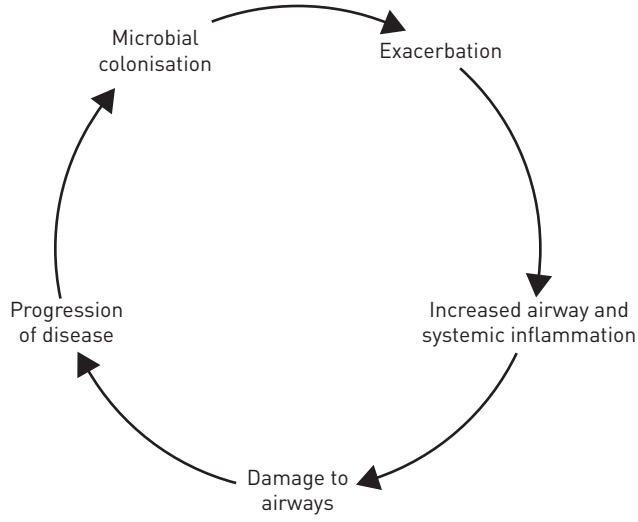

Figure 1. Vicious circle hypothesis of chronic inflammatory pulmonary disorders [6].

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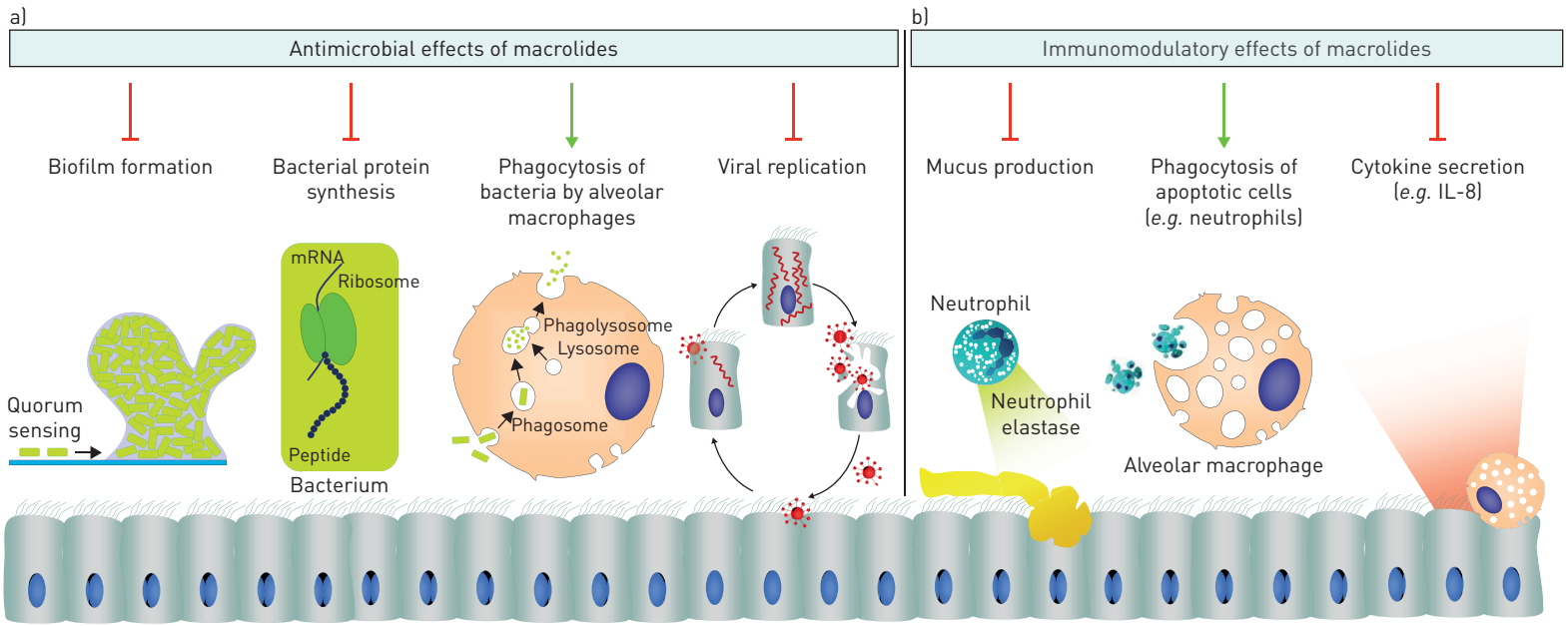

Figure 2. The antimicrobial and immunomodulatory effects of macrolides. a) Antimicrobial effects. Macrolides can directly affect bacteria by inhibiting bacterial protein synthesis, and reducing their adherence and toxin production. In addition, they are able to disrupt biofilm formation through suppression of quorum sensing proteins, in particular in the case of *Pseudomonas aeruginosa* infections. Macrolides stimulate phagocytosis of pathogenic bacteria by alveolar macrophages. In bronchial epithelial cells, they tend to induce antiviral host responses, thereby indirectly hampering viral replication. b) Immunomodulatory effects. Macrolides enhance mucociliary clearance by reducing airway secretions through inhibition of neutrophil elastase and modulation of mucin gene expression, and reduce chronic inflammation by stimulating phagocytosis of apoptotic cells and impairing the production of pro-inflammatory mediators such as IL-8 in airway epithelial cells and alveolar macrophages [53].

https://doi.org/10.1183/2312508X.10005416

Antimicrobial effects of macrolides

The direct antibiotic effect of macrolides is exerted through binding to the bacterial 50S ribosomal subunit, thereby interfering with its assembly and ultimately inhibiting bacterial protein synthesis, leading to a bacteriostatic effect [25, 31, 32]. Their antibacterial spectrum primarily includes the atypical bacteria *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*, and, although resistance is on the increase, Gram-positives such as *Streptococcus pneumoniae*, while the neomacrolides also have a better Gram-negative coverage, including susceptible strains of *Haemophilus influenzae* and *Moraxella catarrhalis* [25, 33, 34]. The neomacrolides clarithromycin and azithromycin have excellent tissue penetration, and hence form the backbone in first-line combination treatment regimens for NTM such as MAC [35, 36]. Acquired resistance to macrolides occurs through alterations in their binding site on the bacterial ribosomal RNA induced by methylases encoded by erythromycin ribosome methylase (*erm*) genes or through macrolide efflux (*mef*) genes encoding for active efflux pumps reducing intrabacterial macrolide concentrations [37, 38].

Indirect antimicrobial effects are established by stimulation of phagocytosis of bacteria by alveolar macrophages [39, 40], and *via* inhibition of quorum sensing and biofilm formation, mechanisms which have been proven particularly useful in reducing the virulence of *Pseudomonas aeruginosa* and facilitating the effects of antipseudomonal antibiotics [41–43]. At subinhibitory concentrations, azithromycin interferes with cell–cell communication through inhibition of the guanosine diphosphomannose dehydrogenase enzyme in the alginate biosynthetic pathway of mucoid *P. aeruginosa* strains, thereby mitigating biofilm production [44]. Interestingly, an increase in the expression level of type III secretion system genes, encoding for virulence factors in *P. aeruginosa*, has also been observed *in vitro*, but up to now without any clinical correlate [44, 45].

Supported by the observation that erythromycin significantly reduced the number of common colds in COPD patients [46], potential antiviral properties of macrolides have also been unravelled more recently [47–49]. *In vitro*, azithromycin decreases viral load in bronchial epithelial cells infected with rhinovirus [49]. Its antiviral effects are possibly mediated by induction of pattern recognition receptors, IFNs and IFN-stimulated genes, leading to a global amplification of the host antiviral response to human rhinoviruses [47, 48]. The antimicrobial effects of macrolides are summarised in figure 2a.

Immunomodulatory effects of macrolides

Long-term treatment courses with 14- and 15-membered-ring macrolides are known to influence chronic airway diseases mediated by neutrophilic inflammation [50–53]. In contrast to other antibiotics that have been attributed immunomodulatory effects, macrolides are known to alter a plenitude of cells within the airway, including neutrophils, alveolar macrophages, lymphocytes and epithelial cells [54, 55]. The pronounced intracellular accumulation and retention of macrolides, and in particular of azithromycin, allows prolongation of their effects within host cells [56, 57]. After an initial stimulation of neutrophil degranulation and phagocytosis-associated oxidative burst enhancing their antibacterial activity, late effects of macrolides include increased neutrophil apoptosis and attenuation of oxidative burst responses [55, 56]. Neutrophilic inflammation is further hampered by macrolide antibiotics through decreased production of chemoattractants and

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decreased expression of adhesion molecules, resulting in attenuation of chemotaxis [58, 59]. Azithromycin may also promote differentiation of monocytoid cell lines into macrophages and alter the macrophage phenotype, leading to reduced secretion of pro-inflammatory cytokines and increased production of anti-inflammatory mediators [60–62]. In addition, macrolides stimulate phagocytosis of apoptotic cells by alveolar macrophages [39, 40], attenuate type 1 T-helper cell (Th1) responses following lipopolysaccharide (LPS)- or IFN-γ-induced stimulation of macrophages, and (although conflicting observations have been reported) seem to affect the balance between Th1 and Th2 responses [63–65].

Additional modulation of host defence occurs through interaction with structural cells, such as bronchial epithelial cells, with beneficial effects on the stability of the epithelial barrier and ciliary function [54, 55]. Macrolide-induced inhibition of neutrophilic elastase and matrix metalloproteinases [66–68], and of respiratory epithelium cytokine production [56, 68, 69], is well established. Most of these effects are probably caused by modulation of mitogen-activated protein kinase and NF-κB signalling pathways [54]. In human airways, epithelial goblet cells and mucous cells synthesise gel-forming mucins such as MUC5AC and MUC5B [54]. Erythromycin and clarithromycin have been shown to inhibit this TNF-α-induced mucus secretion, resulting in improved mucociliary clearance and hence beneficial effects in various clinical conditions characterised by excessive sputum production [51, 70, 71]. The immunomodulatory effects of macrolides are summarised in figure 2b.

Dosing of macrolides

The long half-life and interesting safety profile makes azithromycin the agent of choice for long-term use. When used for its immunomodulatory purposes, azithromycin is typically dosed as 500 mg three times weekly on Monday, Wednesday and Friday (MWF), or alternatively by a daily 250 mg dose, although the AZISAST (Azithromycin in severe asthma) study has shown efficacy in noneosinophilic asthma at lower doses of 250 mg three times weekly [21]. In case of intolerance of the usual dosage, lower doses of 250 mg MWF are worth considering as, although not widely studied, they might have the advantage of inducing less adverse events without losing efficacy. In case of obstinate gastrointestinal intolerance of azithromycin, roxithromycin can be used as an alternative, at a daily dose of 150 mg [72]. As for clarithromycin, most clinical trials have been performed with doses of 500 mg twice daily, although doses as low as 200 mg daily have also proven effective [68, 73].

Other antibiotics

In addition to macrolides, other antibiotics have been investigated, although less intensively, for maintenance treatment in chronic inflammatory airway diseases. Doxycycline and other tetracyclines have been shown to regulate the host immune response, *e.g.* by targeting matrix metalloproteinases released from neutrophils and attenuating LPS-induced inflammation [8, 74, 75]. Immunomodulatory effects have also been attributed to fluoroquinolones, with moxifloxacin selectively inhibiting secretion of cytokines such as IL-8 and IL-6, and NF-κB activation in CF epithelial cell lines, and ciprofloxacin providing anti-inflammatory properties in the setting of LPS-induced lung injury in animal models [76, 77]. In *Stenotrophomonas maltophilia* infection, trimethoprim–sulfamethoxazole (cotrimoxazole) has been shown to suppress TNF-α production by human peripheral blood mononuclear cells [78]. Accumulating *in vitro* evidence suggests that cotrimoxazole is able

to enhance neutrophil chemotaxis, phagocytosis and intracellular killing by macrophages, to reduce lymphocytic proliferation [79]. As mentioned earlier, this chapter will elaborate mainly on the clinical applications of macrolides as only scarce data on the long-term use of other oral antibiotic treatment classes are available.

Long-term oral antibiotic treatment: when and to whom?

Diffuse panbronchiolitis

Diffuse panbronchiolitis is an idiopathic inflammatory disease of the respiratory bronchioles, almost exclusively occurring in Japan and other East Asian countries [80, 81]. This progressive disease is characterised by neutrophilic airway inflammation with elevated pro-inflammatory cytokines such as IL-8 and IL-1β, and often complicated by *H. influenzae* and/or *P. aeruginosa* infection [82, 83]. The prognosis of this possibly fatal disease was significantly improved by the introduction of erythromycin, leading to the suspicion of beneficial effects of erythromycin other than its antibacterial activity [10, 84]. Treatment with macrolides has been shown to decrease BAL fluid levels of neutrophils, IL-8 and pro-inflammatory β-defensins [83, 85, 86]. Nevertheless, most evidence came from retrospective or prospective open trials, suggesting not only efficacy of erythromycin [10, 84, 87, 88], but also of clarithromycin, azithromycin and roxithromycin [73, 89–91]. Only one small RCT was reported examining serial CT scans [92]. As the overt clinical success of macrolide treatment precludes placebo-controlled trials in diffuse panbronchiolitis, the authors of a systematic review instead recommended setting up comparative RCTs between different kinds or doses of macrolides in the future [93].

Cystic fibrosis

CF is a multisystem, autosomal recessive genetic disease, caused by a defect in the CF transmembrane conductance regulator (*CFTR*) gene. Its pulmonary manifestations are characterised by recurrent airway infections, chronic inflammation and progressive lung function decline, resulting in limited life expectancy [94, 95]. However, the prognosis is gradually improving due to the introduction of medication directly targeted to the genetic cause of the disease, as well as treatments directed towards infection and inflammation [96, 97]. Frequent pulmonary exacerbations are known to be associated with increased mortality. Macrolides, which in CF will mainly have anti-inflammatory and antibacterial working mechanisms by inhibiting biofilm formation (figure 2), have been investigated for their potential to improve lung function in CF in five large RCTs (table 1) [11–14, 98]. Forced expiratory volume in 1 s (FEV_1) improved in two studies and azithromycin reduced FEV_1 decline in one study. Although two other trials did not show an effect of macrolides on FEV_1, a reduction in the number of exacerbations was established. The 2012 Cochrane review on macrolide maintenance therapy in CF stated that 6-month azithromycin treatment courses can result in improved FEV_1 and reduced exacerbation rates, but that it is not clear whether this effect will be sustained [99]. What is the effect of treatment with macrolides longer than 12 months [100]? This important issue has recently been addressed in a retrospective study showing that in the 2 years following the first year of azithromycin treatment, the exacerbation rate increased again to levels similar to the period before starting the macrolide [101].

 https://doi.org/10.1183/2312508X.10005416

Table 1. Randomised double-blind placebo-controlled trials with long-term macrolides in cystic fibrosis (CF) and non-CF bronchiectasis

First author [ref.]	Inclusion criteria	Intervention	Length of treatment	Primary outcome	Number of exacerbations
CF					
Saiman [12]	Age ⩾6 years; weight ⩾25 kg; chronic infection with *Pseudomonas aeruginosa*	Azithromycin 250 or 500 mg (weight <40 or ⩾40 kg) three times weekly	168 days	Significantly improved FEV1	Significantly reduced (hazard ratio 0.65)
Clement [11]	Age 6–21 years	Azithromycin 250 or 500 mg (weight <40 or ⩾40 kg) three times weekly	12 months	No significant difference in FEV1	Significantly reduced (rate ratio 0.5)
Equi [13]	Age 8–18 years	Azithromycin 250 or 500 mg (weight <40 or ⩾40 kg) once daily	6 months	Significantly improved FEV1	No significant difference
Wolter [14]	Age ⩾18 years	Azithromycin 250 mg once daily	3 months	Reduced rate of FEV1 decline	No significant difference
Saiman [98]	Age 6–18 years; weight ⩾18 kg; no *Pseudomonas* infection	Azithromycin 250 or 500 mg (weight <36 or ⩾36 kg) three times weekly	168 days	No significant difference in FEV1	50% reduction in exacerbations (hazard ratio 0.5)
Non-CF bronchiectasis					
Wong [15]	Age ⩾18 years; ⩾1 exacerbation requiring antibiotic(s) in preceding year	Azithromycin 500 mg three times weekly	6 months	Significantly reduced number of exacerbations (rate ratio 0.38)	
Serisier [17]	Age 20–85 years; ⩾2 exacerbations requiring antibiotic(s) in preceding year	Erythromycin 400 mg twice daily	48 weeks	Significantly reduced number of exacerbations (rate ratio 0.57)	
Altenburg [16]	Age ⩾18 years; ⩾3 LRTIs requiring antibiotic(s) in preceding year; ⩾1 sputum culture yielding ⩾1 bacterial pathogen in preceding year	Azithromycin 250 mg once daily	52 weeks	Significantly reduced number of exacerbations (rate ratio 0.41)	

FEV1: forced expiratory volume in 1 s.

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To whom?

As macrolides have a positive effect on lung function and exacerbation frequency, it can be suggested to start this treatment in CF patients showing lung function decline or experiencing frequent exacerbations.

Non-CF bronchiectasis

Bronchiectasis is defined as the presence of dilated thick-walled bronchi caused by chronic bronchial inflammation and recurrent airway infections [4]. Many aetiologies have been identified, with the most common causes described in the European Bronchiectasis Registry (EMBARC) being idiopathic (39%) and post-infective (27%). Long-term oral antibiotics were used in 19.4%, consisting mainly (in 74.2%) of azithromycin [102]. One RCT evaluated amoxicillin 3 g twice daily for 32 weeks in bronchiectasis patients expectorating daily purulent sputum, which resulted in a reduction in 24-h sputum volume and purulence, and in symptom awareness [103]. Most recent trials have, however, been examining macrolides mainly based on their anti-inflammatory properties and antibacterial effects by inhibiting biofilm formation (figure 2). The three main randomised double-blind placebo-controlled studies investigating the effect of azithromycin in non-CF bronchiectasis have shown significant reductions in pulmonary exacerbations (table 1) [15–17]. In the trial conducted by Wong *et al.* [15], the benefits of macrolide treatment persisted for 6 months after completion of treatment. Serisier *et al.* [17] showed that low-dose erythromycin also decreased sputum production, with a beneficial effect on lung function, and increased eradication of sputum pathogens.

To whom?

Based on the three trials [15–17], expert opinion supports macrolide maintenance treatment in patients with frequent exacerbations (at least two exacerbations in the previous year) provided their airway clearance techniques have been already optimised. Patients who are stable with good self-reported quality of life and less pulmonary complaints should not be treated with long-term azithromycin [104, 105].

COPD

COPD is defined by progressive airflow obstruction that is poorly reversible and intercurrent acute exacerbations, which have an impact on disease course and mortality risk [3, 106, 107]. Increasing evidence supports an important role for the lung microbiome in the pathogenesis of COPD [108]. Exacerbations are often caused by infectious microorganisms, accompanied by airway and systemic inflammation [109]. Prevention of exacerbations is therefore essential to inhibit further disease progression. During exacerbations, microbiome shifts have been observed, as well as differences related to the exacerbation phenotypes described as bacterial or eosinophilic, with increases in Proteobacteria (mainly *Haemophilus* and *Moraxella* spp.) or Firmicutes (mainly *Streptococcus* spp.), respectively [108, 110]. A UK retrospective cohort study demonstrated that maintenance antibiotic treatment (⩾6 months) had been prescribed only for a small proportion of COPD patients (0.61%). The antibiotics most often used were oxytetracycline, doxycycline and penicillin, with a rise in macrolide prescriptions from 2005 [111].

Many antibiotics have been assessed for long-term treatment in COPD. As early as 1956, an observational study published in *The Lancet* showed overall improvement in 60% of

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patients with chronic bronchitis receiving tetracyclines during 6 months in winter. *H. influenzae* was present in sputum cultures in almost all patients [112]. In contrast, a recent RCT examining a 3-week course of doxycycline in stable COPD patients was not able to show any anti-inflammatory effects [113]. Another observational study published in 1975 showed that an improvement in sputum production and dyspnoea was seen in 50% of COPD patients with chronic sputum production receiving trimethoprim–sulfamethoxazole 960 mg twice daily during 3 months [114]. Recently, intermittent pulsed therapy with moxifloxacin 400 mg once daily for 5 days, repeated each 8 weeks during 48 weeks, reduced the exacerbation rate in COPD patients in an RCT [115].

In addition to their anti-inflammatory functions, macrolides can play a major role in prevention of exacerbations due to their antibacterial and antiviral properties (figure 2). Three major studies have investigated the role of macrolides in reducing exacerbations (table 2). While Uzun *et al.* [18] included patients with frequent exacerbations, patients with nonfrequent exacerbations were also allowed to be enrolled in the other two studies [19, 20]. Macrolides reduced the number of exacerbations in all three trials [18–20]. The beneficial effect of macrolides can be partially explained by the presence of bronchiectasis in patients with COPD. Martínez-García *et al.* [116] showed that bronchiectasis was present in almost 60% of the COPD patients. In the COLUMBUS (COPD: influence of macrolides on exacerbation frequency in patients) trial, CT scans were performed to exclude patients with bronchiectasis [18]. A multicentre RCT examining the effect of short-term macrolide treatment in acute COPD exacerbations is currently ongoing [117].

To whom?

Criteria were proposed for selecting patients for long-term azithromycin treatment. In two reviews, the authors recommend to prescribe macrolides in patients with frequent exacerbations (at least two in the year before treatment) [17, 118]. The most pronounced effect of azithromycin was seen in patients of older age, in those classified in lower Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade and in those not actively smoking [119]. However, this analysis was performed on data which also involved patients with nonfrequent exacerbations.

Severe noneosinophilic asthma

Severe asthma is a heterogeneous syndrome characterised by chronic airway inflammation, either of eosinophilic nature or of noneosinophilic origin (neutrophilic or paucigranulocytic) [120]. In parallel to the chronic neutrophilic airway diseases mentioned previously, the effects of low-dose macrolides have also been examined in patients with severe noneosinophilic asthma [53]. Initially, the observed beneficial effects of macrolides in asthma were attributed to their antimicrobial properties directed towards intracellular pathogens, such as *Chlamydophila* and *M. pneumoniae* [121, 122]. As with respiratory viral infections, infection with and/or reactivation of these atypical bacteria has been associated with both asthma exacerbations and chronic severe asthma [123–125]. Increased susceptibility to infection in asthma probably leads to increased atypical bacterial infection (mainly with *C. pneumoniae*), which itself then further increases neutrophilic airway inflammation by eliciting acute antibody responses such as IgA, leading to aggravation of asthmatic symptoms [124, 125]. Although a partial contribution of their bacteriostatic effects cannot be excluded, it is widely assumed that the immunomodulatory properties of macrolides are the predominant mechanism of action [126, 127]. Whereas shorter-term trials were only able to show some

Table 2. Randomised double-blind placebo-controlled trials with long-term macrolides in COPD and severe asthma

First author [ref.]	Inclusion criteria	Intervention	Length of treatment	Primary outcome
COPD				
Uzun [18]	Age ⩾18 years; ⩾3 exacerbations in the preceding year	Azithromycin 500 mg three times weekly	12 months	Significantly reduced number of exacerbations (rate ratio 0.60)
Albert [19]	Age ⩾40 years; FEV_1 <80% predicted; either use of continuous supplemental oxygen or receipt of systemic corticosteroids within the previous year	Azithromycin 250 mg once daily	12 months	Significantly reduced number of exacerbations (rate ratio 0.83)
Seemungal [20]	FEV_1 30–70% predicted; no exacerbation required	Erythromycin 250 mg twice daily	12 months	Significantly reduced number of exacerbations (rate ratio 0.65)
Severe asthma				
Brusselle [21]	Age 18–75 years; persistent asthma (GINA step 4 or 5); ⩾2 severe asthma exacerbations requiring systemic corticosteroids and/or LRTIs requiring antibiotic(s) within previous year	Azithromycin 250 mg three times weekly	6 months	No difference in rate of severe exacerbations and LRTIs requiring antibiotic(s); significantly reduced number of LRTIs and exacerbations in predefined noneosinophilic severe asthma subgroup (rate ratio 0.43)
Hahn [22]	Age ⩾18 years; persistent asthma	Azithromycin 600 mg weekly	12 weeks (1 year follow-up)	No difference in symptom control, except for open-label group with more severe asthma; not powered to detect differences in exacerbation rate

FEV_1: forced expiratory volume in 1 s; GINA: Global Initiative for Asthma.

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effect of macrolides on reduction of symptoms and improvement of lung function in severe asthma, insufficient to recommend their routine use for asthma control [68, 128–132], the AZISAST study was the first to examine the prevention of exacerbations as a primary end-point in adults with exacerbation-prone severe asthma receiving long-term (6 months) macrolide maintenance therapy (table 2) [21]. In contrast, clinical trials on short-term macrolide treatment in acute asthma exacerbations yielded conflicting results [133–135].

To whom?

In the AZISAST randomised double-blind placebo-controlled trial, low-dose (250 mg three times weekly) azithromycin treatment was only associated with a significant lower exacerbation rate in the predefined subgroup of patients with noneosinophilic severe asthma [21]. The need for a careful selection of patients can also be derived from the AZMATICS (Azithromycin/asthma trial in community settings) trial, where a 12-week macrolide treatment course only showed clinical improvement in an open-label study arm encompassing individuals with severe treatment-resistant or refractory asthma [22]. However, as a recent Cochrane review points out, there is still a need for additional high-quality studies to confirm the possible benefit of macrolides in noneosinophilic severe asthma [136].

Other indications

Azithromycin has also proven useful in bronchiolitis obliterans syndrome (BOS) after lung transplantation [137, 138]. This major complication of lung transplantation is a form of chronic rejection associated with poor survival, defined as a delayed allograft dysfunction with persistent decline in FEV1 without any other known and potentially reversible cause [139, 140]. After encouraging data showing improvements in FEV1 in observational studies [141, 142], Corris *et al.* [143] have recently shown efficacy of azithromycin treatment in improving FEV1 in lung allograft BOS in an RCT. In lung transplant recipients, azithromycin prophylaxis might even prevent the occurrence of BOS [144, 145]. These findings might also be extrapolated to the similar condition of BOS complicating haematopoietic stem cell transplantation; however, the scarce and rather small clinical trials available have not been able to show a significant benefit of azithromycin in this population [146–148].

Organising pneumonia, either cryptogenic, or induced by infections, drug toxicity, vasculitis or other conditions, is an inflammatory disorder characterised by buds of granulation tissue in the peripheral airways and alveoli, preferably treated with systemic corticosteroids [149]. On a case-by-case basis, chronic macrolide treatment may be adjuvant to steroid therapy or act as a steroid-sparing strategy, probably through inhibition of IL-8 release and neutrophil accumulation in the distal airways [150–154].

Long-term oral antibiotic treatment: is it safe?

Drug interactions

Drug interactions of macrolides are mainly mediated by inhibition of hepatic cytochrome CYP (P450) 3A enzymes, but are least pronounced for azithromycin compared with clarithromycin and erythromycin [155]. Through inhibition of CYP3A4, clarithromycin and erythromycin have the propensity of inducing toxic concentrations of a long list of substrates, including most statins, calcium channel blockers, amiodarone and colchicine. As an inhibitor of glycoprotein P, however, azithromycin and the other neomacrolides are able

to increase plasma concentrations of various substrates such as digoxin, everolimus, sirolimus, tacrolimus and posaconazole. All macrolides can cause altered warfarin levels to various extent. Interactions with concomitant medication should therefore always be checked before treatment initiation.

Adverse reactions

To date, no RCTs have thoroughly assessed the long-term safety of chronic macrolide therapy. Typical side-effects include gastrointestinal discomfort such as nausea, diarrhoea and abdominal pain, induced by dose-related effects on motilin receptors [156]. These mild-to-moderate symptoms seldom lead to drug discontinuation (reviewed in [157]) and are less frequently reported with the neomacrolides than with erythromycin [158, 159]. Within the neomacrolides, azithromycin and roxithromycin tend to induce fewer gastrointestinal complaints than clarithromycin.

While severe hepatotoxicity is rare during azithromycin treatment, transient cholestasis or other abnormal liver function tests have been described, although less frequently than with erythromycin [158–160]. Its propensity to induce severe hepatotoxicity excludes telithromycin from long-term treatment indications [28–30]. During long-term azithromycin treatment, monitoring of serum liver enzymes is advisable and treatment should be discontinued immediately if signs or symptoms of hepatitis occur.

The incidence of cardiac events has mainly been monitored in clinical trials on short-term macrolide use [161, 162]. In particular, macrolide antibiotics are known to potentially induce QT prolongation and torsades de pointes [161, 163]. Hence, azithromycin still needs to be used with caution in patients with pre-existing cardiovascular disease and risk factors [164, 165]. Before treatment initiation, measurement of the QT interval by electrocardiography is recommended, in particular in the case of polypharmacy or concomitant treatment with other QT-prolonging drugs such as fluoroquinolones.

Macrolide-induced ototoxicity typically affects the lower (speech) frequencies and is usually characterised by a bilateral sensorineural hearing loss, often reversible [157]. This rare side-effect is dose dependent and facilitated by risk factors such as renal impairment, as was demonstrated in one prospective case–control study in pneumonia patients treated with intravenous erythromycin [166]. Azithromycin-induced hearing loss has been reported in case of long-term high dosage (*e.g.* 500 mg daily) and mostly within a context of treatment of NTM infections [167, 168]. However, its incidence during low-dose long-term treatment still needs to be established [157], although one study in COPD patients observed more hearing decrements in participants receiving azithromycin than in those receiving placebo [19]. While routine audiometric screening is not considered mandatory, some authors suggest ordering audiometry before initiation of therapy in risk groups [169].

Long-term macrolide treatment will undoubtedly have an influence on the respiratory microbiome. A subanalysis of the BLESS (Bronchiectasis and low-dose erythromycin study) trial showed that in patients with non-CF bronchiectasis who were not colonised with *P. aeruginosa*, erythromycin caused a shift in the microbiome from a dominant presence of *H. influenzae* to an increase in concentration of *P. aeruginosa* [17]. Further research on this important area needs to be performed to investigate whether this change in the microbiome will also influence the clinical outcome.

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Macrolide resistance

Prescription of macrolides has been associated with emerging resistance, mainly in *Streptococcus* spp. and *Staphylococcus* spp. [170–174]. Unfortunately, few RCTs assessing long-term macrolide maintenance therapy have monitored for resistance induction. In CF patients, increased macrolide resistance has been observed during long-term macrolide treatment in *Staphylococcus aureus* and *H. influenzae*, particularly after multiple years of therapy [175–178]. As the clinical benefit of azithromycin in CF seems to be limited to the first 6–12 months of treatment [101], implementing shorter treatment courses and periods of treatment interruption might help to tackle resistance development. Similarly, a meta-analysis of RCTs in non-CF bronchiectasis documented an increased risk of macrolide resistance in *H. influenzae*, *S. aureus* and *S. pneumoniae* [179], while COPD trials did not find increased appearance of macrolide-resistant organisms after 3–12 months of therapy [20, 180].

Although macrolide resistance is increasing among pneumococcal isolates, literature on its clinical significance in severe infections such as pneumococcal pneumonia is inconsistent, but does not show a significant increase in mortality [181–184]. A recent retrospective study in a tertiary care hospital found no evidence suggesting that adult patients hospitalised with macrolide-resistant pneumococcal pneumonia experienced a more severe clinical presentation or worse clinical outcome than those with positive cultures for macrolide-susceptible *S. pneumoniae* [185]. From a population point of view, however, it remains important to restrict chronic macrolide use to those patients who will benefit the most in view of the increasing resistance data.

The occurrence of macrolide resistance is facilitated by macrolide monotherapy in the treatment of MAC lung disease and macrolide susceptibility is key to treatment success [186]. As azithromycin is able to block autophagosome clearance by preventing lysosomal acidification in primary human macrophages, leading to impairment of autophagy and, consequently, inhibition of intracellular killing of mycobacteria, some authors fear the induction of (macrolide-resistant) mycobacterial infection during long-term azithromycin use [187]. However, a nested case–control study in one large CF centre recently showed a reduced risk of NTM in CF adults receiving long-term azithromycin, making a plea for its use as primary prophylaxis against NTM [188]. Nevertheless, before initiating macrolide treatment, ideally three sputum samples should be delivered to exclude pre-existing NTM disease in predisposing conditions such as CF and bronchiectasis. Furthermore, current guidelines advise not to continue azithromycin treatment if a positive NTM culture is obtained in CF patients, unless as part of a multidrug treatment regimen in the context of NTM disease [189]. Recommendations for long-term macrolide treatment monitoring are summarised in table 3.

Conclusions

The pleiotropic effects of macrolides such as erythromycin, clarithromycin and azithromycin encompass anti-inflammatory and immunomodulatory capacities, in addition to their antimicrobial effects. The beneficial effects of macrolides have almost unequivocally been accepted in chronic inflammatory airway diseases such as diffuse panbronchiolitis, CF, non-CF bronchiectasis, COPD and severe noneosinophilic asthma (table 4). However, when macrolides are widely used in the community, population antimicrobial resistance will possibly increase. Therefore, indications to start macrolides should be very carefully

Table 3. Recommendations for long-term macrolide treatment monitoring

Adverse events	Timing	Recommendation
Drug hypersensitivity	At start	Absence of known allergy to macrolides
Drug interactions	Any time	Verify concomitant medication
Hepatotoxicity	At start	Aminotransferase levels <3× upper limit of normal
	At 6 weeks	Monitor serum liver enzymes
	Yearly	Monitor liver enzymes (more frequently in risk groups)
Cardiotoxicity	At start	Perform electrocardiography to assess corrected QT interval (<450 ms)
	Any time	Repeat electrocardiography if new concomitant medication influencing QT duration
Ototoxicity	At start	Audiometric screening for pre-existing hearing loss in risk groups (*e.g.* elderly)
NTM infection	At start	Perform sputum samples to exclude pre-existing NTM infection
	6 monthly	Monitor sputum cultures for NTM (particularly in risk groups, *e.g.* cystic fibrosis)

Table 4. Summary of considerations for chronic immunomodulatory therapy with macrolides

Airway disease	Subgroup of patients with expected benefit
Diffuse panbronchiolitis	
CF	Patients with FEV_1 decline and/or frequent (infectious) exacerbations, particularly in case of chronic *Pseudomonas aeruginosa* infection
Non-CF bronchiectasis	Patients with frequent (infectious) exacerbations
COPD	Patients with frequent (infectious) exacerbations
Asthma	Noneosinophilic severe asthmatic patients with frequent exacerbations
Bronchiolitis obliterans	Bronchiolitis obliterans syndrome in lung transplant recipients
Organising pneumonia	Corticosteroid-dependent patients

CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 s.

considered, particularly when used in common diseases such as COPD and asthma, and well monitored (table 3). Azithromycin 500 mg three times weekly (MWF) is the regimen of first choice. In general, long-term macrolides should be considered in the described diseases when patients present with at least two exacerbations per year despite optimal treatment with the ordinary medications as recommended in the relevant guidelines.

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Acknowledgements: The authors would like to thank Ken Bracke and Tania Maes (Dept of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium) for their assistance in designing the figures.

Disclosures: None declared.

Chapter 12

Macrolide therapy for patients with pneumonia: a triple-edged sword

Yuichiro Shindo and Yoshinori Hasegawa

Macrolides, such as azithromycin and clarithromycin, are widely used for the treatment of CAP, and global phase III trials for a novel macrolide, solithromycin, have been completed. Over the past two decades, numerous studies have investigated the effects of macrolides. One of the novel functions of macrolides is their immunomodulatory ability, which suppresses neutrophilic inflammation by decreasing the production of cytokines and other mediators from airway epithelial cells and alveolar macrophages. These immunomodulatory effects may be associated with the effectiveness of macrolides for the treatment of patients with severe CAP. One of the current concerns regarding the adverse effects of macrolides is their cardiovascular toxicity. To avoid macrolide-induced cardiovascular events, physicians should consider the risk factors for QT interval prolongation and cardiac arrhythmias. In this chapter, we summarise the available evidence regarding the beneficial and adverse effects of macrolides, discuss their role in the treatment of pneumonia and highlight the remaining clinical questions to be addressed in future studies.

Cite as: Shindo Y, Hasegawa Y. Macrolide therapy for patients with pneumonia: a triple-edged sword. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 206–231 [https://doi.org/10.1183/2312508X.10005516].

Pneumonia is one of the leading causes of death due to an infectious disease throughout the world [1]. During the past century, multiple antibiotics have been developed since penicillin was discovered in 1929, benefiting countless patients [2]. Since erythromycin was discovered in 1952, more than 300 new macrolide antibiotic candidates have been synthesised [3] and macrolide therapy has contributed to improving the outcomes of patients with various infectious diseases. In particular, azithromycin and clarithromycin are widely used for the treatment of CAP [4, 5]. More recently, two global phase III trials of solithromycin (a novel macrolide antibiotic) for the treatment of CAP have been completed [6, 7]. For patients with CAP, the causative pathogens that are frequently identified include atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila* (*Chlamydia*) *pneumoniae* and *Legionella pneumophila*, in addition to *Streptococcus pneumoniae*,

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Haemophilus influenzae and *Moraxella catarrhalis* [4, 8]. One of the important effects of macrolides is their antimicrobial activity against these atypical pathogens. Therefore, the atypical coverage provided by macrolides has been considered to play an important role in the treatment of CAP [9].

Macrolides have multipotent beneficial effects that include both antimicrobial activity and immunomodulatory effects. The first study to reveal the mechanistic role of macrolides as immunomodulatory agents was reported from Japan: KUDO *et al.* [10] revealed that the mortality of patients with diffuse panbronchiolitis was dramatically improved by low-dose erythromycin therapy. Subsequently, additional evidence has been presented regarding the mechanisms of the immunomodulatory action of macrolides, rather than the antibacterial effects.

Similar to other antibiotics, macrolides also exhibit some adverse effects. It has been found that the main reactions to macrolides include hepatotoxicity and gastrointestinal toxicity (*e.g.* diarrhoea, nausea and vomiting). Although less frequent, physicians should be aware that macrolide therapy can also increase the risk of potential adverse cardiovascular events and life-threatening arrhythmias [11]. Thus, while macrolide therapy has beneficial antimicrobial and immunomodulatory properties, it is also associated with cardiovascular toxicity and physicians should consider macrolides to be "triple-edged swords" when considering their risks and benefits.

The aim of this chapter is to: 1) summarise the available evidence regarding the multidimensional effects of macrolides pertaining to both the beneficial and adverse effects, 2) discuss the implications of macrolide therapy for patients with pneumonia in future practice, and 3) consider the type of future research needed in areas where there is insufficient evidence, in order to resolve the remaining questions in the present clinical settings.

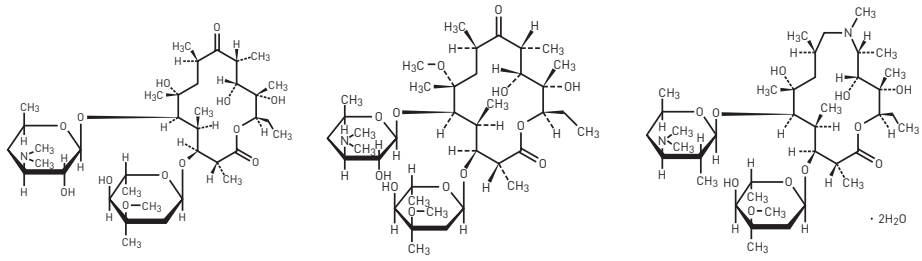
Novel actions of macrolides: evidence from basic research

In the treatment guidelines for patients with pneumonia, the recommended macrolides include clarithromycin and azithromycin, which have 14- and 15-membered lactone rings, respectively (figure 1) [4, 5]. Their antibacterial mechanism of action involves binding to the 50S subunit of bacterial ribosomes. Subsequently, transpeptidation, translocation, chain elongation and bacterial protein synthesis are inhibited [12, 13]. The antibacterial mechanism of action of azithromycin and clarithromycin is similar to that of an older macrolide, erythromycin (figure 1). However, erythromycin lacks antimicrobial activity against *H. influenzae* [4]. More importantly, the reason that macrolides may be preferred to other antibiotics is that they exhibit immunomodulatory effects in addition to antibacterial functionality. During the past two decades, numerous studies have shown that macrolides can serve as immunomodulators in both infectious and noninfectious respiratory diseases in animal models, as well as in humans. In the following, we discuss the novel actions of macrolides against three different targets with regard to host defence and antimicrobial functions. The possible mechanisms modulated by macrolides are summarised in figure 1.

Modulation of immune cell functions

The discovery by KUDOH *et al.* [10] that low-dose, long-term macrolide therapy was efficacious in patients with diffuse panbronchiolitis was one of the important triggers

Structural formulae of representative macrolides



Erythromycin Clarithromycin Azithromycin

Modulation of immune cell functions

Neutrophils
- ▼ Recruitment and migration
- ▼ ROS production
- ▼ Elastase production

T-cells
- ▼ Proliferation
- ▼ Cytokine production: Th1 (IL-2, TNF-α and IFN-γ); Th2 (IL-4, IL-5, IL-10 and IL-13); Th17 (IL-17)
- ▼ Chemotaxis
- ▲ Apoptosis

B-cells
- ▼ Expression of the costimulatory molecules CD40, CD80 and CD86

Macrophages
- ▼ Pro-inflammatory cytokine production (*e.g.* IL-1β, IL-6, IL-8, TNF-α and GM-CSF)
- ▼ NO production
- ▲ Phagocytosis of apoptotic neutrophils (efferocytosis)

Dendritic cells
- ▼ Pro-inflammatory cytokine production (IL-6, IL-12p40 and TNF-α)
- ▲ Anti-inflammatory cytokine production (IL-10)

Modulation of epithelial and endothelial cell functions

Airway epithelial cells
- ▲ Transepithelial electrical resistance (tight junction barrier)
- ▲ β-Defensin-1 and -2
- ▲ IgA production and neutralising activities in airway mucosa
- ▲ Ciliary function
- ▼ Sputum production
- ▼ Mucus secretion
- ▼ Adhesion molecule expression
- ▼ Pro-inflammatory cytokine production
- ▼ Inflammatory mediators

Vascular endothelial cells
- ▼ Angiogenesis
- ▼ Adhesion molecule expression

Effects of antimicrobial functions

Streptococcus pneumoniae
- ▼ Pneumolysin production

MRSA
- ▼ Coagulase activity

Pseudomonas aeruginosa
- ▼ Adherence
- ▼ Virulence factors
- ▼ Biofilm formation
- ▼ Quorum sensing

Figure 1. Structure and novel actions of macrolides. The structural formulae of erythromycin, clarithromycin and azithromycin are presented as representative macrolide antibiotics. Macrolides with 14- and 15-membered lactone rings have novel actions against three different targets, in addition to their well-known antibacterial effects. ROS: reactive oxygen species; Th: T-helper cell; CD: cluster of differentiation; GM-CSF: granulocyte–macrophage colony-stimulating factor; NO: nitric oxide.

suggesting that macrolides exhibit functions other than antibacterial properties. In addition, it has been shown that invasion of inflammatory cells can be dampened by the use of macrolide therapy [14, 15]. This anti-inflammatory effect was found to be induced by the inhibition of pro-inflammatory cytokine production and the expression of adhesion molecules *via* the direct action of macrolides on various cell types [14, 15]. These effects could be potential key mechanisms in the prevention of acute lung injury in patients with pneumonia.

 https://doi.org/10.1183/2312508X.10005516

Neutrophils

Neutrophils are important effector cells of the innate immune system during pulmonary infections, killing microbes by phagocytosis, the secretion of antimicrobials and neutrophil extracellular traps [16]. Neutrophils also influence other cells of the innate and adaptive immune system, generating a variety of immune mediators to direct specific immune responses. However, neutrophils release cytotoxic products, such as elastase and reactive oxygen species (ROS), that can result in tissue damage [16–18]. Therefore, neutrophils are necessary for host defence, but can also be harmful during pulmonary infections.

One of the primary anti-inflammatory activities of macrolides is modulation of the pro-inflammatory activities of neutrophils, especially the inhibition of IL-8 production, which is a potent neutrophil activator and chemoattractant [15, 19, 20]. As shown in figure 1, neutrophil migration is also inhibited by macrolides. The mechanisms of action of macrolides include the following: 1) decreased production of IL-1β and TNF-α by macrophages and other structural cells [21, 22], 2) decreased expression of adhesion molecules (*e.g.* soluble intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and macrophage adhesion molecule-1) on vascular endothelial cells, airway epithelial cells and neutrophils [21, 22], and 3) interference with the production of metalloproteinases by fibroblasts and neutrophils *via* the inhibition of activation of NF-κB and activator protein (AP)-1 [23–25]. Other anti-inflammatory interactions between macrolides and neutrophils include the inhibition of ROS and elastase production from these cells [14, 15, 26, 27]. It has been reported that the inhibitory effect on ROS production by macrolides is partially due to cell membrane stabilisation, including attenuation of the membrane-destabilising effect of bioactive phospholipids, such as lysophosphatidylcholine, platelet-activating factor (PAF) and lyso-PAF [28]. Regarding the decreased in elastase production, macrolides have previously been suggested to have anti-elastolytic properties in inflamed airways [27].

Lymphocytes

Macrolides can affect the effector functions of lymphocytes (figure 1). It has been reported that macrolides can inhibit T-cell function regarding the production of T-helper cell type 1 (Th1) cytokines (*e.g.* IL-2, TNF-α and IFN-γ) and Th2 cytokines (*e.g.* IL-4, IL-5, IL-10 and IL-13) by interfering with the activation of intracellular signalling, such as *via* the c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) pathways, as well as by transcriptional factor NF-κB [15]. A previous study also revealed that macrolides suppress IL-17 production *via* the direct modulation of mammalian target of rapamycin (mTOR) activity [29]. The above intracellular signalling pathways, including JNK, ERK, NF-κB and mTOR, are associated with reduced proliferation of T-cells [15]. Macrolides affect both the chemotaxis and apoptosis of T-cells [15, 30–32]. Moreover, Asano *et al.* [33] reported that expression of the costimulatory molecules CD40, CD80 and CD86 on B-cells was decreased by roxithromycin.

Monocytes and macrophages

Macrolides interact directly with monocytes and macrophages. Previous studies have revealed that macrolides suppress the production of pro-inflammatory cytokines (*e.g.* IL-1β, IL-6, IL-8, TNF-α and granulocyte–macrophage colony-stimulating factor (GM-CSF)) with decreased cytokine gene expression due to the suppressed activation of intracellular signalling (*i.e.* mitogen-activated protein kinase (MAPK) and ERK pathways) and transcription factors (*e.g.* NF-κB and AP-1) [15, 34–42]. Macrolides also suppress the production of nitric oxide (NO), associated with decreased inducible NO synthase in

pulmonary alveolar macrophages [14, 43, 44]. It has also been shown that macrolides enhance the efferocytosis of neutrophils by human alveolar macrophages [45, 46].

Dendritic cells

Dendritic cells (DCs) play an important role as antigen-presenting cells. A previous study revealed that azithromycin induced the production of the anti-inflammatory cytokine IL-10 from bone marrow-derived DCs in mice and that clarithromycin suppressed the production of IL-6 [47]. Macrolides also suppressed the production of pro-inflammatory cytokines, including IL-6, IL-12p40 and TNF-α, by bone marrow-derived DCs in an animal model of chronic *Pseudomonas aeruginosa* airway infection, as well as by monocyte-derived DCs in human peripheral blood [47–49].

Modulation of epithelial and endothelial cell functions

Airway epithelial cells

The airway epithelium functions not only as a mechanical barrier, but also as a source of multiple microbicidal agents and chemical mediators in the airway surface liquid [14, 50]. In patients with pneumonia, the airway epithelial cells are potentially one of the main targets of macrolide immunomodulatory effects.

Macrolides can decrease mucus secretion by inhibiting the chloride channels on airway epithelial cells and by decreasing the expression of MUC5AC, a gel-forming mucin in the human airway, through the inhibition of ERK1/2 and IκBα activation [14, 51–53]. In addition, macrolides can activate the ciliary function of airway epithelial cells [54, 55], as well as enhancing IgA production and neutralising activities in the airway mucosa through the induction of IgA class switching, recombination and the upregulation of B-cell-activating factor of the TNF family in mucosal DCs [56]. Asgrimsson *et al.* [57] reported that azithromycin increased transepithelial electrical resistance (tight junction barrier), while Ishizawa *et al.* [58] revealed that erythromycin increased the production of human β-defensin-1 and -2 mRNA and protein, which are components of innate immunity produced by epithelial cells in the airway. Adhesion molecule expression (*e.g.* ICAM-1) is also decreased by macrolides [14].

Airway epithelial cells are important producers of multiple pro-inflammatory cytokines and inflammatory mediators [14]. It has been found that macrolides can inhibit intracellular signalling pathways (*e.g.* MAPK and IκB–NF-κB), resulting in interference of the activation of transcriptional factors such as NF-κB and AP-1 [14, 59]. These mechanisms of action also lead to a reduction in pro-inflammatory cytokines (*e.g.* IL-8, TNF-α, IL-6 and GM-CSF [39, 60–63]) and inflammatory mediators [64, 65]. The reduced pro-inflammatory cytokine and mediator production are associated with suppression of excessive neutrophilic inflammation.

Vascular endothelial cells

The initial phase of neutrophil migration prior to activation in the lung parenchyma is an important point when planning interventions for the prevention of lung injury. Li *et al.* [66] reported that 14-membered lactone ring macrolides attenuated the expression of VCAM-1 mRNA during the early phase in a model of bleomycin-induced lung injury. This could be one of the immunomodulatory effects of macrolides in pneumonia. Macrolides also reduce angiogenesis, which is associated with lesion formation in chronic inflammation with inhibition of vascular endothelial growth factor production [14].

 https://doi.org/10.1183/2312508X.10005516

Effects of antimicrobial functions

The novel effects of macrolides for the treatment of bacterial infections include the inhibition of adherence, virulence factors, biofilm formation and quorum sensing (figure 1) [14].

S. pneumoniae

S. pneumoniae is the most frequently identified pathogen in patients with CAP [4, 67, 68]. Pneumolysin is an exotoxin produced by *S. pneumoniae* and is important for its pathogenicity [69, 70]. FUKUDA *et al.* [71] revealed that macrolides reduced the activity of pneumolysin and improved the survival rates in macrolide-treated animal models of pneumococcal pneumonia compared with the control animals. The authors stressed that this survival benefit of macrolides was shown in an animal model of macrolide-resistant *S. pneumoniae* pneumonia [71].

MRSA and P. aeruginosa

MRSA and *P. aeruginosa* are the representative causative pathogens of nosocomial pneumonia [72]. *Staphylococcus aureus* has multiple virulence factors, including coagulase, which is an exotoxin. YANAGIHARA *et al.* [73] reported that the coagulase activity of MRSA was decreased by macrolides. *P. aeruginosa* also has many factors that affect its pathogenicity. It has been reported that macrolides have inhibitory effects on the twitching motility of *P. aeruginosa* and suppress its quorum sensing, which is associated with pathogenicity and biofilm formation [74]. However, future studies are required to validate these clinical effects in pneumonia patients infected with these pathogens.

Implications of combination therapy with macrolides: evidence from clinical research

Over the past two decades, numerous studies have investigated the effects of empirical therapy, particularly antibiotic combination therapy, with or without a macrolide [75–105]. These findings are summarised in tables 1–3.

Therapeutic effects of macrolides for patients with CAP

Table 1 summarises previous observational studies that have attempted to assess the therapeutic effects of macrolides in overall hospitalised patients with CAP. In several studies, the definition of CAP included patients with nursing home-acquired pneumonia. As shown in table 1, five out of the nine studies reported that combination therapy with a β-lactam plus a macrolide significantly reduced mortality compared with β-lactam monotherapy [75–79]. In contrast, four observational studies reported that a significant difference in the 30-day or in-hospital mortality was not shown between the β-lactam plus macrolide combination therapy and the β-lactam monotherapy groups [80–82]. ASPA *et al.* [82] also reported that β-lactam plus macrolide combination therapy was inferior to levofloxacin monotherapy. Thus, both positive and negative results on the beneficial effects of macrolide use were reported in these studies of overall inpatients with CAP. However, there were some trends when the results of studies were compared between patients with nonsevere and severe CAP (table 2).

Table 1. Therapeutic effects of macrolides in overall hospitalised patients with CAP

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Gleason [77]	1999	USA	Observational, retrospective, multicentre	CAP	Elderly (age ⩾65 years), inpatients	Ward and ICU	Comparison of 12 regimens (reference β-lactam monotherapy)	30-day mortality	Lower 30-day mortality in patients who received BLM combination therapy	Yes
Houck [76]	2001	USA	Observational, retrospective, multicentre	CAP[#]	Elderly (age ⩾65 years), inpatients	Ward and ICU	Comparison of eight regimens including BLM combination therapy *versus* β-lactam monotherapy	30-day mortality	Lower 30-day mortality in patients who received BLM combination therapy	Yes
García Vázquez [75]	2005	Spain	Observational, retrospective analysis of prospectively collected data, single centre	CAP	Inpatients	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	In-hospital mortality	Lower in-hospital mortality in patients who received BLM combination therapy	Yes
Loh [80]	2005	Malaysia	Observational, prospective, single centre	CAP	Inpatients	Ward and ICU	Macrolide therapy *versus* nonmacrolide therapy	In-hospital mortality	No difference in in-hospital mortality between the two treatment groups (not adjusted)	No

Continued

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Table 1. Continued

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Aspa [82]	2006	Spain	Observational, prospective, multicentre	CAP#	Pneumococcal pneumonia	Ward and ICU	Comparison of five regimens (reference BLM combination therapy)	30-day mortality	No significant difference in 30-day mortality among the regimens, but BLM combination therapy was inferior to levofloxacin monotherapy in patients with PSI class >III	No
Paul [81]	2007	Israel, Germany and Italy	Observational, prospective, multicentre	CAP#	Inpatients	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	30-day mortality	No significant difference in 30-day mortality between the two treatment groups	No
Lodise [92]	2007	USA	Observational, retrospective, multicentre	CAP	Inpatients	Ward and ICU	BLM combination therapy *versus* fluoroquinolone	14- and 30-day mortality	No difference in 14-day and 30-day mortality between the two treatment groups	No

Continued

Table 1. Continued

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Tessmer [79]	2009	Germany	Observational, prospective, multicentre	CAP#	Inpatients	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	14- and 30-day mortality	Lower 14-day mortality in patients who received BLM combination therapy, but no difference in 30-day mortality between the two regimens	Yes
Rodrigo [78]	2013	UK	Observational, prospective, multicentre	CAP#	Inpatients	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	30-day mortality	Lower 30-day mortality in patients who received BLM combination therapy	Yes

Articles were reviewed using PubMed with the search terms "macrolide AND (community-acquired pneumonia OR nursing home-acquired pneumonia OR (healthcare-associated pneumonia OR health-care-associated pneumonia) OR nosocomial pneumonia OR hospital-acquired pneumonia OR ventilator-associated pneumonia)" with the language limitation "English". We also cite papers that were related to macrolide therapy or antibiotic combination treatment with macrolides. Studies in which the macrolide combination effect was not assessed were excluded. From the results, we selected studies that assessed the effects of macrolides among total patients with CAP. BLM: β-lactam plus macrolide; PSI: Pneumonia Severity Index. #: including pneumonia coming from long-term care facilities.

https://doi.org/10.1183/2312508X.10005516

Table 2. Effects of macrolides in nonsevere and severe CAP

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Nonsevere pneumonia/non-ICU patients										
Burgess [86]	2000	USA	Observational, retrospective, multicentre	CAP[#]	Inpatients, non-ICU	Ward	BLM combination therapy *versus* β-lactam monotherapy	Mortality	No difference in mortality between the two treatment groups	No
Dudas [83]	2000	USA	Observational, prospective, multicentre	CAP[#]	Inpatients	Ward	BLM combination therapy *versus* β-lactam monotherapy	Mortality	Lower mortality in patients who received BLM combination therapy in the non-ICU setting	Yes
Brown [84]	2003	USA	Observational, retrospective, multicentre	CAP	Inpatients, non-ICU	Ward	BLM combination therapy *versus* β-lactam monotherapy	30-day mortality	Lower 30-day mortality in patients who received BLM combination therapy (not adjusted)	Yes
Bratzler [85]	2008	USA	Observational, retrospective, multicentre	CAP	Inpatients, non-ICU	Ward	Comparison of nine regimens (reference β-lactam monotherapy)	30-day mortality	Lower 30-day mortality in non-ICU patients who received BLM combination therapy or fluoroquinolone monotherapy	Yes

Continued

Table 2. Continued

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Garin [88]	2014	Switzerland	Open-label, noninferiority, randomised, multicentre	CAP	Inpatients, nonsevere pneumonia[¶]	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	Primary: clinical stability at day 7; secondary: readmission, mortality, *etc.*	No statistically significant difference in reaching clinical stability between the two treatment groups, but lower in BLM combination therapy (p=0.07); 30-day readmission rate was significantly lower in BLM combination therapy	No for primary end-point; yes for 30-day readmission
Postma [87]	2015	Netherlands	Cluster-randomised crossover, noninferiority, multicentre	CAP	Inpatients, non-ICU	Ward	Comparison of three regimens (BLM combination therapy, β-lactam monotherapy and fluoroquinolone) (reference β-lactam monotherapy)	90-day mortality	No significant difference in 90-day mortality among the three treatment groups	No
Severe pneumonia, bacteraemia or ICU patients										
Dudas [83]	2000	USA	Observational, prospective, multicentre	CAP[#]	Inpatients	ICU	BLM combination therapy *versus* β-lactam monotherapy	Mortality	No difference in mortality between the two treatment groups in the ICU setting	No

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Table 2. Continued

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Martinez [96]	2003	Spain	Observational, retrospective analysis of prospectively collected data, single centre	CAP and nosocomial pneumonia	Bacteraemic pneumococcal pneumonia	Ward and ICU	Macrolide therapy *versus* nonmacrolide therapy	In-hospital mortality	Lower in-hospital mortality in patients who received macrolide therapy	Yes
Weiss [90]	2004	USA	Observational, retrospective, single centre	CAP	Inpatients, bacteraemic pneumococcal pneumonia	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	Mortality	Lower mortality in patients who received BLM combination therapy compared with patients who received β-lactam monotherapy	Yes
Dwyer [95]	2006	Sweden, USA, Spain, UK and Canada	Observational, retrospective analysis of prospectively collected data, multicentre	CAP[#]	Bacteraemic pneumococcal pneumonia	Ward and ICU	BLM combination therapy *versus* β-lactam monotherapy	Mortality	No significant difference in mortality between the two treatment groups	No
Mufson [91]	2006	USA	Observational, retrospective, multicentre	Unclear description	Bacteraemic pneumococcal pneumonia	Ward and ICU	Comparison of three regimens (BLM combination therapy, β-lactam monotherapy and β-lactam monotherapy +nonmacrolides)	Mortality	Lower mortality in patients who received BLM combination therapy (not adjusted)	Yes
Rodriguez [93]	2007	Spain	Observational, retrospective analysis of prospectively collected data, multicentre	CAP	Inpatients, admission to ICUs	ICU	BLM combination therapy *versus* monotherapy including β-lactam monotherapy and fluoroquinolone	28-day in-ICU mortality	Lower mortality rate in patients who received BLM combination therapy compared with monotherapy	Yes

Continued

Table 2. Continued

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Metersky [99]	2007	USA	Observational, retrospective, multicentre	CAP#	Inpatients, bacteraemic pneumonia	Ward and ICU	With or without atypical coverage	In-hospital and 30-day mortality	Lower in-hospital and 30-day mortality in patients who received atypical coverage with a macrolide	Yes
Lodise [92]	2007	USA	Observational, retrospective, multicentre	CAP	Inpatients, PSI class V	Ward and ICU	BLM combination therapy *versus* fluoroquinolone	14- and 30-day mortality	Lower mortality in patients who received BLM combination therapy in PSI class V	Yes
Bratzler [85]	2008	USA	Observational, retrospective, multicentre	CAP	Inpatients, admission to ICUs	ICU	Comparison of nine regimens (reference β-lactam monotherapy)	30-day mortality	Aminoglycosides increased risk for mortality, but otherwise no difference in 30-day mortality between treatment groups	No
Blasi [94]	2008	Italy	Interventional, before-and-after study, multicentre	CAP#	Inpatients, PSI classes IV and V	Ward	Comparison of five regimens (reference β-lactam monotherapy)	Mortality during first treatment	Lower mortality during first treatment in patients with PSI classes IV and V who received BLM combination therapy or fluoroquinolone monotherapy	Yes

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Table 2. Continued

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Restrepo [97]	2009	USA	Observational, retrospective, multicentre	CAP	Inpatients, severe sepsis	Ward and ICU	Macrolide therapy *versus* nonmacrolide therapy	30- and 90-day mortality	Lower mortality rate in patients who received macrolide therapy	Yes
Martin-Loeches [100]	2010	Nine European countries	Observational, prospective, multicentre	CAP	Inpatients, admission to ICUs, requiring invasive mechanical ventilation	ICU	Combination therapy with a macrolide *versus* combination therapy with a fluoroquinolone	ICU mortality and 30-day mortality	Lower mortality rates in patients who received combination therapy with a macrolide	Yes
Naucler [98]	2013	Sweden	Observational, retrospective, multicentre	CAP	Bacteraemic pneumococcal pneumonia	Ward and ICU	Comparison of six regimens (reference β-lactam monotherapy)	30-day mortality	Lower 30-day mortality in patients who received BLM combination therapy or fluoroquinolone	Yes

The search strategy is described in table 1. From the results, we selected studies that assessed the effects of macrolides in each patient group with nonsevere and severe CAP. BLM: β-lactam plus macrolide; PSI: Pneumonia Severity Index. [#]: including pneumonia coming from long-term care facilities; [¶]: patients with nonsevere pneumonia included those who did not meet the 2007 Infectious Diseases Society of America/American Thoracic Society criteria [4] or who were not classified into PSI class V.

https://doi.org/10.1183/2312508X.10005516

Table 3. Effects of macrolides in patients with pneumonia at risk for drug-resistant pathogens

First author [ref.]	Year	Country	Study design	Pneumonia category	Specific inclusion criteria	Site	Comparison	Outcome parameter	Results (summary of findings)	Significant beneficial effect of macrolides
Gleason [77]	1999	USA	Observational, retrospective, multicentre	Pneumonia coming from long-term care facilities	Elderly (age ⩾65 years), inpatients	Ward and ICU	Comparison of 12 regimens (reference β-lactam monotherapy)	30-day mortality	No significant difference in 30-day mortality among regimens	No
Laserna [104]	2014	USA	Observational, retrospective, multicentre	CAP	Inpatients, CAP due to *Pseudomonas aeruginosa*	Ward and ICU	Macrolide therapy *versus* nonmacrolide therapy	90-day mortality	No significant difference in 30-day mortality between the two treatment groups	No
McEvoy [103]	2014	USA	Observational, retrospective, single centre	Healthcare-associated pneumonia[#]	Inpatients	Ward and ICU	Macrolide therapy *versus* nonmacrolide therapy	In-hospital mortality	No significant difference in in-hospital mortality between the two treatment groups	No
Giamarellos-Bourboulis [105]	2008	Greece	Double-blind, randomised trial, multicentre	VAP	Inpatients	ICU	Antibiotic therapy with a macrolide *versus* without a macrolide (placebo control)	Primary: number of days until resolution of VAP; secondary: number of days receiving mechanical ventilation and 28-day mortality	Clarithromycin accelerated the resolution of VAP and weaning from mechanical ventilation in surviving patients and delayed death in those who died of sepsis; 28-day mortality was not altered	Yes for primary end-point; no for mortality

The search strategy is described in table 1. From the results, we selected studies that assessed the effects of macrolides among inpatients with CAP due to *Pseudomonas aeruginosa*, healthcare-associated pneumonia and VAP. [#]: healthcare-associated pneumonia was defined as pneumonia co-occurring with hospitalisation for ⩾2 days during the preceding 90 days, residence in a nursing home or extended care facility, home intravenous therapy (including antibiotics and chemotherapy), chronic dialysis during the preceding 30 days or home wound care during the preceding 30 days.

https://doi.org/10.1183/2312508X.10005516

Effects of macrolides for patients with nonsevere CAP

Studies on the use of macrolides for inpatients with nonsevere CAP or those who were not admitted to an ICU found conflicting results (table 2) [83–88]. A retrospective study by Burgess *et al.* [86] showed no difference in mortality between patients who received antibiotic treatment with and without a macrolide. However, three observational studies, including one prospective and two retrospective ones, found positive results for antibiotic regimens involving a macrolide that were significantly associated with reduced mortality [83–85]. Recently, two research groups performed RCTs [87, 88]. Garin *et al.* [88] assessed the clinical stability of patients 7 days after the initiation of therapy (the primary end-point) between the β-lactam plus macrolide combination therapy and β-lactam monotherapy groups of patients with nonsevere CAP. The proportion of patients reaching clinical stability on day 7 tended to be lower in the β-lactam plus macrolide combination therapy group than in the β-lactam monotherapy group (33.6% *versus* 41.2%, respectively; p=0.07). In addition, the 30-day readmission proportion was significantly lower in the combination therapy group than in the monotherapy groups (3.1% *versus* 7.9%, respectively; p=0.01) [88]. In contrast, Postma *et al.* [87] compared three different regimens comprising β-lactam plus macrolide combination therapy, β-lactam alone and fluoroquinolone alone in non-ICU settings. They showed no significant differences in the 90-day mortality between the three treatment groups and β-lactam monotherapy did not result in a longer length of hospital stay or a higher incidence of complications. Therefore, the effect of the addition of macrolides may be minimal for patients with nonsevere CAP.

Effects of macrolides for patients with severe CAP

The trends for the effects of macrolide use in patients with severe CAP or bacteraemia, or in those who require ICU admission, are likely to differ from those with nonsevere CAP (table 2). Although the majority of the studies were observational and there were few RCTs [83, 85, 89–100], this should not be a focus of criticism when taking into account the difficulties of performing interventional studies (*e.g.* RCTs in critical care settings). Only three studies did not shown a benefit of a combination therapy of macrolides on mortality compared with β-lactam monotherapy [83, 85, 95]. In contrast, 10 studies showed that empirical therapy with macrolides or combination therapy with a β-lactam plus a macrolide significantly reduced mortality in patients with bacteraemic pneumonia [90, 91, 96, 98, 99] and in those with severe pneumonia or those who required ICU admission [92–94, 97, 100]. Importantly, Restrepo *et al.* [97] revealed that macrolide therapy was associated with a lower mortality rate in patients with severe sepsis due to pneumonia and macrolide-resistant pathogens, while Yanagihara *et al.* [101] also reported that macrolides might be effective for patients with macrolide-resistant *S. pneumoniae* pneumonia. These findings may be associated with the immunomodulatory effects of macrolides, as described in a previous section. Thus, macrolides are likely to be effective for patients with severe CAP and bacteraemia.

Effects of macrolides on patients with pneumonia and at risk for drug-resistant pathogens

Compared with studies on CAP, there are a limited number of studies that have focused on the therapeutic effects of macrolides in patients with pneumonia who are at risk for drug-resistant pathogens (DRPs), including nursing home-acquired pneumonia, nosocomial pneumonia (*e.g.* VAP) and CAP due to nosocomial pathogens (*e.g. P. aeruginosa*). To date, it has been thought that the efficacy of macrolides was questionable, as atypical pathogens were not frequently identified in patients with pneumonia at risk for DRPs [67, 102].

However, the results of previous studies that demonstrated the beneficial effects of macrolides for patients with severe CAP and their immunomodulatory effects led to the hypothesis that macrolides may also be beneficial for patients with pneumonia who are at risk for DRPs. The available study results are summarised in table 3. Gleason *et al.* [77] performed a retrospective multicentre observational study and conducted a subanalysis for patients from long-term care facilities. They reported that there was no significant difference in 30-day mortality among the antibiotic regimens. More recently, McEvoy *et al.* [103] investigated the effect of antibiotic therapy with or without a macrolide in patients with CAP and healthcare-associated pneumonia. In this retrospective study, for patients with healthcare-associated pneumonia, the in-hospital mortality for the macrolide therapy group tended to be lower than that in the nonmacrolide therapy group (adjusted OR 0.81, 95% CI 0.65–1.01), although statistical significance was not reached. Laserna *et al.* [104] performed an interesting study on patients with CAP due to *P. aeruginosa* and showed that there was no significant difference in 30-day mortality between the macrolide and nonmacrolide therapy groups. Regarding nosocomial pneumonia, Giamarellos-Bourboulis *et al.* [105] performed an RCT on patients with VAP to investigate the effects of antibiotic therapy with or without a macrolide. They revealed that clarithromycin accelerated the resolution of VAP and weaning from mechanical ventilation in the surviving patients, and also delayed death in those who died of sepsis. However, the 28-day mortality remained unaltered. Therefore, from the currently available evidence, the therapeutic effects of macrolides may be lower in patients with pneumonia who are at risk for DRPs compared with those with CAP, especially those with severe CAP.

Effects of macrolides on immune functions in patients with pneumonia

As described in a previous section, basic research has revealed that macrolides have immunomodulatory effects. Two recent studies using clinical samples showed interesting results for pro-inflammatory cytokine levels, although the sample sizes were relatively small [106, 107]. Lorenzo *et al.* [106] prospectively investigated 52 hospitalised patients with CAP who developed an inadequate initial response. After 72 h of antibiotic administration, patients who received macrolide therapy exhibited lower levels of IL-6 and TNF-α in their BAL fluid, lower IL-8 and IL-10 in the blood, and reached clinical stability more rapidly compared with those who received nonmacrolide therapy. Arnold *et al.* [107] showed that CAP patients treated with a macrolide exhibited trends of lower levels of IL-6, IL-8 and IFN-γ from day 5 to day 7 following the initiation of therapy compared with those treated without a macrolide. These findings suggest that macrolide therapy may have anti-inflammatory effects for patients with pneumonia.

Adverse effects of macrolides

The common side-effects of macrolides include hepatotoxicity and gastrointestinal toxicity (*e.g.* nausea, diarrhoea and abdominal pain). The most significant adverse effects consist of QT interval prolongation and cardiovascular events. The newer macrolides exhibit a greater tolerance than the older macrolide erythromycin. Erythromycin was the first macrolide to be associated with QT interval prolongation. The rank order of arrhythmogenicity potential is considered to be: erythromycin>clarithromycin>roxithromycin>azithromycin [108, 109]. Currently, there is great concern regarding the cardiovascular toxicity resulting from macrolide therapy in patients with pneumonia.

 https://doi.org/10.1183/2312508X.10005516

QT interval prolongation and cardiovascular events associated with macrolide therapy

Ray *et al.* [11] performed a large database analysis of adults aged 30–74 years in the USA, and investigated the association between administration of azithromycin and risk of cardiovascular death. In this study, patients taking azithromycin for 5 days had an increased risk of cardiovascular mortality (hazard ratio (HR) 2.88, 95% CI 1.79–4.63) and all-cause mortality (HR 1.85, 95% CI 1.25–2.75) compared with patients who did not take antibiotics. Relative to amoxicillin, azithromycin was associated with an increased risk of cardiovascular death (HR 2.49, 95% CI 1.38–4.50) and all-cause mortality (HR 2.02, 95% CI 1.24–3.30). Case reports and other studies have also suggested an association between treatment with azithromycin and an increased risk of cardiovascular morbidity and mortality [110, 111]. Therefore, in 2013, the US Food and Drug Administration issued a warning regarding the risk of QT interval prolongation and potentially fatal torsades de pointes [112].

Other large cohort studies have shown conflicting results [113, 114]. Svanstrom *et al.* [114] conducted a nationwide historical cohort study involving Danish adults (aged 18–64 years) and revealed that current azithromycin use was not associated with an increased risk of death due to cardiovascular causes compared with the use of penicillin V (rate ratio 0.93, 95% CI 0.56–1.55). Mortensen *et al.* [113] evaluated the association of azithromycin with mortality and cardiovascular events among elderly patients with pneumonia in a large cohort of US veterans. In this study, the 90-day mortality was significantly lower in patients who received azithromycin compared with those who received other guideline-concordant antibiotic therapy (17.4% *versus* 22.3%; OR 0.73, 95% CI 0.70–0.76). However, patients who received azithromycin were slightly more likely to have a myocardial infarction (5.1% *versus* 4.4%; OR 1.17, 95% CI 1.08–1.25), but azithromycin was not associated with the risk of overall cardiac events, cardiac arrhythmias or heart failure. Thus, although this issue remains under debate, physicians should consider the risks and benefits of macrolide therapy during prescribing decisions [111].

Risk factors for QT interval prolongation and development of cardiac arrhythmias following macrolide administration

An important consideration for physicians is to understand the risk factors for cardiac arrhythmias and cardiovascular events in patients who require macrolide therapy. Table 4 shows the possible risk factors for these events following macrolide administration [110, 111, 115–118]. Another factor for physicians to note is that such cardiotoxicity can be caused by both macrolides and antibiotics (*e.g.* fluoroquinolones) [111, 117]. According to a systematic review of case reports in which azithromycin was administered, all 12 cases with azithromycin-associated QT interval prolongation and torsade de points were associated with at least two risk factors [110]. Therefore, patients with multiple risk factors as presented in table 4 may be considered at risk for developing cardiovascular events. For these patients, physicians should carefully review their electrocardiograms and subsequently determine antibiotic regimens based on the potential risks and benefits. Further studies on the predictive rule for the development of cardiac arrhythmias and cardiovascular events are required.

Future issues

When considering future treatment strategies for patients with pneumonia, there are a number of associated clinical questions.

Table 4. Possible risk factors for QT interval prolongation and development of cardiac arrhythmias after macrolide therapy

Elderly
Female
Genetic factors
Congenital long QT syndrome
Unidentified channelopathies
Metabolic abnormalities
Hypokalaemia
Hypomagnesaemia
Hypercalcaemia
Acute hypercarbia and hypoxia
Hyperlipidaemia
Underlying cardiac diseases
Existing QT interval prolongation
History of torsades de pointes
Significant bradycardia
Bradyarrhythmia
Use of certain antiarrhythmic drugs
Class IA (*e.g.* quinidine and procainamide)
Class III (*e.g.* dofetilide, amiodarone and sotalol)
Atrial fibrillation
Uncompensated heart failure
Myocardial ischaemia and infarction
Cardiomyopathies
Existing factors when taking other medications, with risk of QT prolongation without dose adjustment
Renal or hepatic insufficiency
Use of inhibitors of the cytochrome P450 3A isozymes
Genetic polymorphisms
Administration of multiple drugs with QT liability

Information from [110, 111, 115–118].

Which patients would benefit from combination therapy with a macrolide among patients with pneumonia?

Recently, it has been considered that the treatment categories for patients with pneumonia should be divided into two major groups [72]: 1) community-onset pneumonia, including CAP and pneumonia coming from the community in patients at risk for DRPs [67, 119–122], and 2) patients with HAP and VAP [72]. For community-onset pneumonia, one possible future treatment strategy is to consider the risk factors for DRPs, including *P. aeruginosa*, ESBL-producing *Enterobacteriaceae* and MRSA (figure 2). Patients with community-onset pneumonia at low risk for DRPs are good targets for usual CAP therapy, such as β-lactam monotherapy, a combination of a β-lactam plus a macrolide or fluoroquinolone monotherapy. According to recent evidence, any of the three usual CAP therapies could be acceptable for patients with nonsevere pneumonia and at low risk for developing DRPs [87]. In contrast, patients with severe pneumonia and at low risk for DRPs would be an optimal target for combination therapy with a β-lactam plus a macrolide. To confirm these hypotheses, validation studies are required, as the majority of the studies shown in tables 1–3 were performed in CAP patients and did not include a sample of patients with unknown DRP status. For patients at high risk for DRPs, including community-onset pneumonia, HAP and

 https://doi.org/10.1183/2312508X.10005516

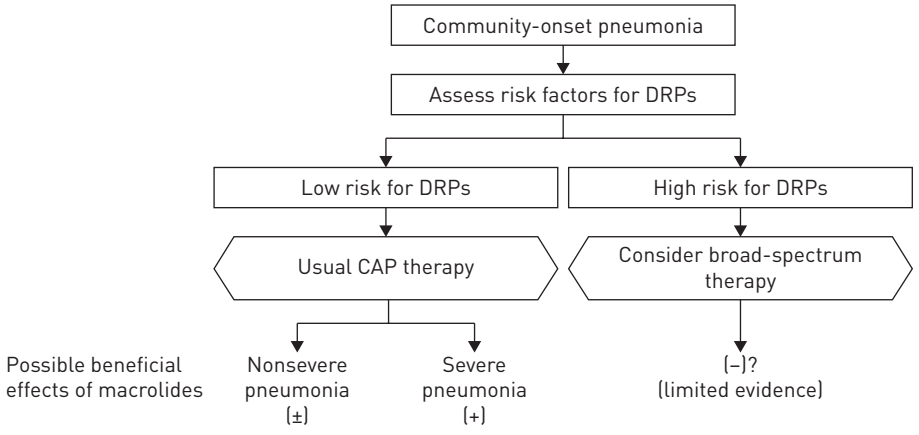

Figure 2. Treatment algorithm for patients with community-onset pneumonia. Local factors should be taken into consideration when assessing risk factors for drug-resistant pathogens (DRPs). Representative DRPs include *Pseudomonas aeruginosa*, ESBL-producing *Enterobacteriaceae* and MRSA. Usual CAP therapy is combination therapy with a β-lactam plus a macrolide, or monotherapy with a β-lactam or a fluoroquinolone.

VAP, the available data have not demonstrated a benefit of macrolides due to a lack of supportive evidence. Thus, future studies are needed for these patients.

Is solithromycin effective and safe in patients with severe CAP?

Two global phase III studies with solithromycin (a novel fluoroketolide related to 14-membered lactone ring macrolides) have recently been completed: SOLITAIRE-IV (a randomised double-blind multicentre study to evaluate the efficacy and safety of intravenous to oral solithromycin (CEM-101) compared with intravenous to oral moxifloxacin in the treatment of adult patients with community-acquired bacterial pneumonia) and SOLITAIRE-ORAL (a randomised double-blind multicentre study to evaluate the efficacy and safety of oral solithromycin (CEM-101) *versus* oral moxifloxacin in the treatment of adult patients with community-acquired bacterial pneumonia) [6, 7]. In these studies, it was shown that solithromycin monotherapy was equivalent to moxifloxacin monotherapy for patients with mild to moderate community-acquired bacterial pneumonia. In addition, the percentage increase in the QT interval was lower in the solithromycin group than in the moxifloxacin group [7]. Compared with telithromycin, solithromycin was 2-fold more potent against pneumococci *in vitro*, including macrolide-resistant strains and *H. influenzae*, and was extremely active against atypical pathogens [123]. Similar to other macrolides, solithromycin exhibits anti-inflammatory effects [124]. However, as mentioned previously, macrolides such as azithromycin, combined with a β-lactam, are likely to be more effective in patients with severe CAP compared with those with mild to moderate CAP. Therefore, clinical trials of combination therapy with solithromycin should be performed in patients with severe CAP to confirm its efficacy and safety.

How should we use two different anti-inflammatory agents: corticosteroids and macrolides?

This may be one of the biggest concerns for physicians. However, to the best of our knowledge, there is no available evidence to answer this question. Torres *et al.* [125]

reported the beneficial effect of corticosteroids for CAP patients who have a high inflammatory status (CRP >150 $mg{\cdot}L^{-1}$). Future research is therefore required to investigate the following issues in clinical settings: 1) the combination or synergistic effect of corticosteroids plus a macrolide, 2) factors associated with beneficial effects of corticosteroids, macrolides or a combination of the two and 3) the immunological characteristics of the patients for whom corticosteroids or macrolides were ineffective. Recently, our research group identified five risk factors for 30-day mortality in patients with community-onset pneumonia who received appropriate initial antibiotic treatment (*i.e.* patients with hypoalbuminaemia, nonambulatory status, acidaemia, tachypnoea and high blood urea nitrogen concentration) [126]. When patients have multiple risk factors, they are at increased risk for mortality, despite receiving appropriate antibiotic treatment. Therefore, adjunctive therapy other than antibiotics (*e.g.* immunomodulators) is important to improve patient outcome. Such patients affected by multiple risk factors for mortality may be good targets for evaluating the effects of corticosteroids and macrolides.

Conclusions

Macrolide antibiotics exhibit multidimensional effects, similar to a triple-edged sword. Two associated beneficial effects of macrolides are antibacterial and immunomodulatory actions, but macrolides also have the potential to cause adverse effects, especially cardiotoxicity. During the last two decades, numerous studies have shown that macrolides can play a role as immunomodulators in both acute and chronic pulmonary diseases. These immunomodulatory actions, including the suppression of neutrophilic inflammation, in addition to antibacterial effects, may be associated with the clinical evidence that macrolide therapy is likely to be effective for patients with severe pneumonia. However, to avoid macrolide-induced cardiovascular events, physicians should understand the risk factors for QT interval prolongation and cardiac arrhythmias. Moreover, patients with multiple risk factors could be at increased risk for adverse cardiovascular events. For such cases, refraining from macrolides should be considered, especially for patients with nonsevere pneumonia. Macrolide effects and the risk stratification of DRPs (*i.e. P. aeruginosa* and MRSA) should also be considered when refining the treatment strategy of patients with pneumonia. Future studies that investigate the various immunomodulatory effects of corticosteroids and macrolides are also required.

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Disclosures: Y. Shindo has received personal fees from Pfizer, Shionogi, Beckman Coulter, MSD, Dainippon Sumitomo Pharma and Taisho Toyama Pharmaceutical. Y. Hasegawa has received grants from Chugai Pharmaceutical, Daiichi Sankyo, Astellas Pharma Dainippon Sumitomo Pharma and MSD. He has also received personal fees from Taisho Toyama Pharmaceutical, Shionogi, Pfizer, Chugai, Daiichi Sankyo, Astellas Pharma, Dainippon Sumitomo Pharma, MSD, Meiji Seika Pharma and Abbott Japan.

Chapter 13

Treatment options for MDR- and XDR-TB

Kwok Chiu Chang[1] and Giovanni Sotgiu[2]

TB is a relevant clinical and public health threat. The annual decline in the incidence rate of TB has been hindered by the emergence and spread of MDR-TB, as well as by TB/HIV co-infection. In 2014, the estimated incidence and mortality of MDR-TB were 480 000 and 190 000, respectively. The highest estimates were provided by China, India and former Soviet Union countries. MDR-TB is the result of human activities, and its proportion is more relevant in previously treated than in new TB cases. However, in several geographical settings, the percentage of MDR-TB among new TB cases is increasing following the transmission of MDR *Mycobacterium tuberculosis* strains. The current treatment success rate is poor (~50%), in association with a therapeutic armamentarium that is not highly effective, safe or cheap. New (*e.g.* bedaquiline, delamanid) and repurposed (*e.g.* linezolid, clofazimine) drugs are recommended to improve the treatment outcome of difficult-to-treat MDR-TB patients. New therapeutic strategies (*e.g.* shorter regimens) can achieve better results.

Cite as: Chang KC, Sotgiu G. Treatment options for MDR- and XDR-TB. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 232–244 [https://doi.org/10.1183/2312508X.10005616].

Caused by *Mycobacterium tuberculosis*, TB is an important clinical and public health issue worldwide. The World Health Organization (WHO) estimated that 9.6 million people developed TB disease and 1.5 million people died from TB in 2014 [1]. The WHO DOTS (directly observed treatment, short course) strategy, which aimed to decrease the global TB burden, achieved important successes in terms of morbidity and mortality reductions [2–4]. Unfortunately, this was offset by the impact of TB/HIV co-infection, particularly in sub-Saharan Africa. Individuals with a weakened immune system developed the disease, thereby increasing the transmission of TB to susceptible close contacts. Furthermore, over the last decade, the emergence and spread of MDR-TB has had a devastating effect on the prognosis of TB patients co-infected by HIV [5–8]. Building on the WHO DOTS Strategy, the WHO Stop TB Strategy was launched in 2006 to introduce new measures for combating TB/HIV co-infection and MDR-TB [9].

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-083-5. Online ISBN: 978-1-84984-084-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Definition and epidemiology of MDR- and XDR-TB

MDR-TB is defined as TB with *in vitro* resistance to isoniazid and rifampicin, which are essential first-line anti-TB drugs [1]. MDR-TB implies a substantial reduction in effective and safe therapeutic options.

In 2014, 480 000 (range 360 000–600 000) new cases of MDR-TB were identified and 190 000 (range 120 000–260 000) MDR-TB patients died worldwide [1]. The percentages of MDR-TB cases among new and previously treated TB patients were 3.3% and 20.0%, respectively [1]. The majority of MDR-TB cases were concentrated in India, China and former Soviet Union countries. In some geographical settings, the percentage of MDR-TB cases among new and previously treated TB patients can be >30% and >50%, respectively [1]. The amplification of drug resistance, which occurs as a result of the selection of drug-resistant mutants with increasingly more severe drug resistance, adds to the complexity of MDR-TB.

About a decade ago, the term "extensively drug-resistant" (XDR)-TB was coined to describe MDR-TB with additional resistance to any fluoroquinolones and at least one second-line injectable drug (amikacin, kanamycin or capreomycin) [1, 10–12]. XDR-TB represents ∼10% of the total MDR-TB cases. In 2007, "totally drug-resistant" (TDR)-TB was used to describe a few cases of XDR-TB patients with drug resistance to all tested anti-TB drugs. TDR-TB has not been recognised universally owing to the lack of a consensus regarding anti-TB drugs that should be included in the definition and the poor reliability of drug susceptibility testing (DST) for second-line drugs [13, 14].

Treatment outcomes for MDR-TB

A systematic review, published in 2012, that carried out a meta-analysis of individual patient data succinctly described and analysed the outcomes of conventional MDR-TB treatment [15]. A total of 9153 MDR-TB patients were enrolled from 32 observational studies carried out in 23 countries located in all WHO regions. The review reported treatment success in 4934 (54%) patients, default/transfer out/unknown in 2095 (23%), death in 1392 (15%), failure in 645 (7%) and relapse in 87 (1%). The treatment success rate varied according to the drug resistance pattern: it was 64% for those with bacillary susceptibility to any quinolones and second-line injectables, 56% for those with bacillary resistance to second-line injectables, 48% for those with bacillary resistance to fluoroquinolones, and 40% among XDR-TB cases. The low success rate could be explained partly by the low proportion of patients treated with fluoroquinolones, particularly later-generation fluoroquinolones. Subgroup analysis among patients with XDR-TB also showed that the failure or death rate varied according to the drug resistance pattern: it was 35% among XDR-TB cases without additional drug resistance, and 49% among XDR-TB cases with additional resistance to pyrazinamide, ethambutol and group 4 drugs [16, 17]. Only 5% underwent surgical treatment and 21% suffered from at least one adverse event. Poor treatment outcomes were frequent among subgroups with previous anti-TB drug exposure, advanced disease or TB/HIV co-infection. Use of quinolones, prothionamide/ethionamide and cycloserine (second-line drugs other than those in group 5) was associated with treatment success, whereas the administration of an increasing number of group 5 drugs (an indication of more severe drug resistance) was associated with a poor treatment outcome. The conclusions reached were that the drug resistance pattern, number of prescribed drugs and respective treatment duration in the intensive and continuation phases affected MDR-TB treatment

outcome. As a result, it is considered crucial to prescribe at least four effective drugs in the intensive phase (more than six for XDR-TB patients) and three effective drugs during the continuation phase (four for XDR-TB) of MDR-TB treatment. The total treatment duration should last between 20 and 25 months, with the intensive phase lasting 7–9 months. The results of the systematic review, while they were in preparation, formed the backbone of the WHO updates on MDR-TB treatment in 2011 [18]. An MDR-TB treatment regimen should include the following: pyrazinamide, a fluoroquinolone (preferably later generation), a second-line injectable drug (kanamycin, amikacin or capreomycin), ethionamide/prothionamide and cycloserine or *p*-aminosalicylic acid. The outpatient model of care is preferred over the hospital-based model. Early antiretroviral therapy (within the first 2 months) is strongly recommended in TB/HIV co-infected patients, irrespective of the $CD4^+$ cell count.

Since the 2011 WHO MDR-TB treatment guidelines were promulgated, global MDR-TB treatment outcomes have not improved substantially, possibly because of underdiagnosis, drug unavailability and other factors that have affected effective implementation of the guidelines. There have also been concerns about uncertain treatment effectiveness, poor adherence to the long anti-TB therapy, and severe and frequent adverse events. Poor adherence is associated with poor treatment outcomes (*e.g.* death, failure, default), infectiousness and amplification of drug resistance.

The WHO recently released new MDR-TB treatment guidelines to address existing MDR-TB management issues, with an emphasis on rapid molecular tests for second-line drugs and recommendations for using shorter MDR-TB regimens for carefully selected subgroups, which made reference to several studies conducted among predominantly MDR-TB treatment-naive patients [19–23]. The shorter MDR-TB regimen consists of four core drugs (moxifloxacin, clofazimine, ethambutol and pyrazinamide) given throughout (9–12 months), supplemented by prothionamide, kanamycin and high-dose isoniazid in the initial 4–6 months. Its main advantages are the short overall duration and affordability. However, the new regimen should be restricted to individuals who have not been exposed previously to second-line drugs and in settings where resistance to one or more drugs in the shorter regimen is unlikely, which can be difficult to ascertain in some settings with a high prevalence of drug resistance to components of the shorter regimen, especially when DST results for pyrazinamide, ethambutol, clofazimine and prothionamide can be unreliable. Epidemiological data retrieved from drug resistance surveys or surveillance systems should provide information on the feasibility of the new regimen. An empirical approach should be avoided as far as possible, with treatment modified by reliable DST results where appropriate. Whenever possible, timely detection of drug resistance should rely on genetic methods (*i.e.* identification of genetic mutations associated with resistance).

With the availability of effective repurposed agents and novel anti-TB drugs, new clinical trials are needed to evaluate new anti-TB regimens and to demonstrate their efficacy, safety and tolerability.

Repurposed agents

Linezolid and clofazimine have been "repurposed" for treating MDR-TB. Developed in the 1950s as an anti-TB drug but then used predominantly for leprosy, clofazimine has re-emerged as a drug for treating MDR-TB since the 1990s [24–26]. Released in 2000 and

 https://doi.org/10.1183/2312508X.10005616

initially approved for the treatment of Gram-positive bacterial infection, linezolid has been used off-label against MDR-TB. The WHO has recognised linezolid and clofazimine as core drugs (group C) in the treatment of MDR-TB [19].

Linezolid

With an MIC (inhibiting 90% of dominant strains) of 0.5 $mg{\cdot}L^{-1}$, a mutant prevention concentration (inhibiting 90% of mutants) of 1.2 $mg{\cdot}L^{-1}$ and *in vivo* activity against MDR-TB treatment in mice, linezolid had been used off-label for MDR-TB with promising efficacy [27–29]. Among patients with fluoroquinolone-resistant MDR-TB, use of linezolid significantly improves sputum culture conversion, cure or treatment completion rates [30, 31].

To achieve stable cure of fluoroquinolone-resistant MDR-TB with a linezolid-based treatment regimen, it is often necessary to prescribe linezolid throughout the treatment course [32]. However, the initial experience with long-term administration of linezolid was frequently complicated by excessive inhibition of mitochondrial protein synthesis, which clinically manifested as anaemia, thrombocytopenia and peripheral/optic neuropathy [29, 33]. The safety profile of linezolid warrants its use in fluoroquinolone-resistant MDR-TB [31, 34].

The optimal linezolid dosing schedule remains open. Reducing linezolid dosage from 600 mg twice daily to 600 mg once daily can significantly reduce adverse events [34]. Further reducing the dosage to 300 mg once daily can additionally reduce adverse events, except for the risk of neuropathy, with possible concerns about acquiring drug resistance [30, 35]. Three-times-weekly dosing shortens exposure to linezolid levels that critically suppress mitochondrial protein synthesis, thereby preventing or ameliorating neuropathy [32]. Therapeutic drug monitoring may help to reduce toxicity, as evidenced by a significant association between adverse events and mean linezolid trough levels >2 $mg{\cdot}L^{-1}$ [35]. Linezolid may be used in the presence of renal disease without dosage adjustment [36].

Cost has limited the large-scale use of linezolid. Generic linezolid may increase drug accessibility, which has been further promoted by the inclusion of linezolid in the WHO Model List of Essential Medicines (www.who.int) since 2015.

Linezolid is being evaluated in a number of phase II or III MDR-TB drug trials, which include NiX-TB, MDR-END and TB-PRACTECAL (table 1) [37].

Clofazimine

Murine TB models have demonstrated that clofazimine could shorten first-line TB treatment and sustain cure of MDR-TB with a low relapse rate of 7% after treatment for 8–9 months [38, 39]. The "Bangladesh regimen" used predominantly for treating MDR-TB treatment-naive patients has reaffirmed the rekindled interest in "repurposing" clofazimine against MDR-TB [20]. The shorter MDR-TB regimen containing clofazimine has been used successfully in at least three other cohorts of predominantly MDR-TB treatment-naive patients [21–23]. A retrospective cohort study in South Africa found a significant association between use of clofazimine and improved culture conversion among XDR-TB patients with HIV co-infection [40]. An RCT in China among pulmonary non-XDR MDR-TB patients, all given pyrazinamide and other second-line drugs according to medication history and DST, demonstrated that clofazimine could promote cavity closure,

Table 1. Currently registered phase II or III MDR-TB drug trials involving use of repurposed agents or novel drugs

Trial registry identifier (trial name)[#]	Repurposed agents or novel drugs	Phase	Description
NCT02354014	Bedaquiline	II	Evaluation of the pharmacokinetics, safety, tolerability and antimycobacterial activity of bedaquiline in combination with MDR-TB therapy for HIV-uninfected children and adolescents
ISRCTN78372190 (STREAM I)	Clofazimine	III	Comparison of the standard WHO MDR-TB regimen with 9-month modified Bangladesh regimen
NCT02409290 (STREAM II)	Bedaquiline, clofazimine	III	Comparison of a 6- and 9-month bedaquiline-containing regimen against the WHO and Bangladesh regimens
NCT02454205, PACTR201409000848428 (NEXT)	Bedaquiline, linezolid	III	Open-label RCT of a 6–9-month injection-free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/ high-dose isoniazid and pyrazinamide
NCT02333799 (NiX-TB)	Bedaquiline, pretomanid[¶], linezolid	III	Study of bedaquiline, pretomanid and linezolid in patients with XDR- and MDR-TB for 6 months with an option of 9 months
NCT02193776 (NC-005)	Bedaquiline, pretomanid	II	Study of 8-week treatment combining bedaquiline, pretomanid and pyrazinamide for drug-sensitive TB, and moxifloxacin, bedaquiline, pretomanid and pyrazinamide for MDR-TB patients
NCT02342886 (STAND)	Pretomanid	III	Efficacy, safety and tolerability of a combination of moxifloxacin, pretomanid and pyrazinamide treatments after 6 months of treatment in subjects with MDR-TB compared with a combination of moxifloxacin, pretomanid and pyrazinamide treatments in drug-sensitive TB subjects; there will be a comparator arm for MDR-TB
NCT02583048 (ACTG A5343)	Bedaquiline, delamanid	II	Study of drug–drug interactions and combined QT effects of bedaquiline and delamanid
NCT01424670	Delamanid	III	Safety and efficacy study of delamanid or placebo for 6 months in combination with optimised background therapy for 18–24 months

Continued

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Table 1. Continued

Trial registry identifier (trial name)[#]	Repurposed agents or novel drugs	Phase	Description
NCT01859923	Delamanid	II	Safety, efficacy and pharmacokinetics study of delamanid in paediatric patients with MDR-TB
NCT02619994 (MDR-END)	Delamanid, linezolid	II	Comparing the efficacy of a treatment regimen including delamanid, linezolid, levofloxacin and pyrazinamide for 9–12 months, with a control arm of the standard treatment regimen including injectables for 20–24 months for the treatment of quinolone-sensitive MDR-TB
NCT02607449	FS-1	III	Safety and efficacy of FS-1 in oral dosage form in drug-resistant pulmonary TB
NCT02365623	Bedaquiline	II	An open-label single-arm multicentre trial to explore the safety, efficacy and pharmacokinetics of bedaquiline in Japanese participants with pulmonary MDR-TB
NCT02754765 (endTB)	Bedaquiline, delamanid	III	An open-label, noninferiority multicountry RCT evaluating the efficacy and safety of new combination regimens for MDR-TB treatment
NCT02589782 (TB-PRACTECAL)	Bedaquiline, pretomanid, linezolid, clofazimine	II–III	A multicentre open-label multiarm RCT evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed anti-TB drugs for the treatment of biologically confirmed pulmonary MDR-TB

WHO: World Health Organization. [#]: ClinicalTrials.gov (https://clinicaltrials.gov), ISRCTN Registry (www.isrctn.com) or Pan African Clinical Trials Registry (www.pactr.org); [¶]: also known as PA-824. Information from [37].

enhance culture conversion and improve treatment success rates [41]. Despite the findings from the South African cohort study and the Chinese RCT, clofazimine may depend on pyrazinamide for its activity, as evidenced by frequently observed treatment failure among fluoroquinolone-resistant (often also pyrazinamide-resistant) MDR-TB patients, in contrast to better outcomes among treatment-shortening studies involving a large number of MDR-TB treatment-naive patients [20–23].

Clofazimine can induce bedaquiline resistance, possibly by upregulating a multisubstrate efflux pump [42], thereby potentially jeopardising the subsequent use of bedaquiline in a salvage regimen.

Initially dosed up to 300 mg daily, clofazimine is now generally used at a dosage of 100 mg daily. A murine TB model has suggested that clofazimine may be effective for TB treatment at much lower doses [43].

Besides prolonging the QT interval, the side-effects of clofazimine are mainly cutaneous (hyperpigmentation, dry skin, pruritus, rash, photosensitivity, eye irritation), gastrointestinal (diarrhoea, rarely bowel obstruction) and neurological (giddiness, taste disturbance).

Clofazimine is being evaluated in a number of phase II or III MDR-TB drug trials, including STREAM I, STREAM II and TB-PRACTECAL (table 1) [37].

Novel drugs

Novel anti-TB drugs have been reviewed comprehensively [27, 44]. The better-known ones that have entered phase II and III trials include bedaquiline, delamanid, pretomanid, sutezolid and SQ109. Here, we focus on bedaquiline and delamanid, which are the only two that have been formally approved for conditional use in the treatment of carefully selected MDR-TB patients [27, 44], and pretomanid, which has entered phase III trials but has not yet been approved by regulatory agencies.

Bedaquiline

In December 2012, the US Food and Drug Administration conditionally approved the use of the diarylquinoline bedaquiline (also known as TMC207 and Sirturo) for treating adult pulmonary MDR-TB when an effective treatment regimen cannot otherwise be provided [45, 46]. In March 2014, the European Medicines Agency made a similar decision [47]. Although not routinely recommended, bedaquiline can also be considered for use in individual patients with extrapulmonary TB, children, pregnant women, or persons with HIV or other comorbid conditions when treatment options are limited [46]. Following consideration of the excess deaths and QT interval prolongation in a placebo-controlled trial [48], bedaquiline is administered with black box warnings about a higher risk for death (nine out of 79 *versus* two out of 81 patients) and possible synergistic cardiotoxic effects regarding its use with other QT interval-prolonging drugs (*e.g.* fluoroquinolones, clofazimine, delamanid and macrolides) [46].

By inhibiting mycobacterial ATP synthase and depleting intracellular ATP, bedaquiline acts on both actively replicating and dormant mycobacteria [49]. Bedaquiline resistance rates are predictable, with a spontaneous mutation rate of approximately 1 in 10^7 to 1 in 10^8 in the wild-type H37Rv strain (similar to that of rifampicin) [50]. Apart from cross-resistance with clofazimine, possibly due to upregulation of a multisubstrate efflux pump [42], there is no cross-resistance between bedaquiline and other anti-TB drugs.

The efficacy of bedaquiline was established by three MDR-TB phase IIb trials [46]. Owing to a long half-life with extensive tissue distribution, bedaquiline is administered at 400 mg once daily in the first 2 weeks and then at 200 mg three times weekly for 22 weeks [46]. The extremely long terminal elimination half-life (6 months) and intracellular drug accumulation have raised concerns about bedaquiline monotherapy and acquired drug resistance among those lost to follow-up. Despite faster culture conversion and significant

 https://doi.org/10.1183/2312508X.10005616

early bactericidal activity in phase II trials, and high rates of culture conversion in XDR-TB patients, the 120-week culture conversion rate among patients with pre-XDR-TB and XDR-TB in a single-arm trial of a bedaquiline-based regimen were only 70.5% and 62.2%, respectively [51–53]. Measures are thus needed to minimise the amplification of drug resistance among patients with XDR-TB.

Bedaquiline is generally well tolerated and rarely results in drug withdrawal [51–53]. Metabolised by cytochrome P450 3A4 (CYP3A4), it can be used without dosage adjustment among patients with mild to moderate renal impairment [46]. The main safety concerns include QT interval prolongation, which may signify cardiotoxicity, possible sudden cardiac death and hepatotoxicity [46]. No relationship could be demonstrated between bedaquiline serum levels or Fridericia-corrected QT (QTcF) >500 ms and survival outcome [46]. Bedaquiline induces phospholipidosis [54], but its implications are unclear. Hepatotoxicity may occur, as suggested by an elevation of alanine transaminase, which was observed more frequently among patients given bedaquiline than those given placebo (7.7% *versus* 2.5%) [48].

Clinicians should minimise the use of other QT interval-prolonging drugs as far as possible, consider levofloxacin instead of moxifloxacin when prescribing a fluoroquinolone, monitor electrocardiography and correct electrolyte disturbance. Drug–drug interactions *via* CYP3A4 have precluded the prolonged use of bedaquiline with moderate to potent CYP3A4 inducers (*e.g.* rifampicin, rifapentine, efavirenz, etravirine, carbamazepine, phenytoin and St John's wort) [55, 56] and moderate or strong CYP3A4 inhibitors (*e.g.* ciprofloxacin, macrolides, fluconazole, ketoconazole and ritonavir) [56]. The WHO has provided guidance for the safe implementation of bedaquiline at a programmatic level [57, 58].

Bedaquiline is being evaluated in a number of phase II or III MDR-TB drug trials, which include NCT02354014, STREAM II, NEXT, NiX-TB, NC-005, NCT02583048, NCT02365623, endTB and TB-PRACTECAL (table 1) [37].

Delamanid

Delamanid (also known as OPC-67683 and Deltyba) is the second novel drug licensed for treating adult pulmonary MDR-TB. In November 2013, the European Medicines Agency approved the conditional use of delamanid for pulmonary MDR-TB.

Delamanid is a nitroimidazopyran (nitroimidazo-oxazole) derived from metronidazole. It is thus contraindicated in persons with metronidazole allergy. Like isoniazid, delamanid is a pro-drug that kills aerobically by inhibiting mycolic acid biosynthesis. Activation requires a deazaflavin-dependent nitroreductase. Delamanid resistance is associated with mutation in the *ddn* gene encoding the deazaflavin-dependent nitroreductase. With a spontaneous mutation rate of approximately 1 in 10^5 in the wild-type H37Rv strain, delamanid is more prone to the development of bacillary resistance than rifampicin or moxifloxacin; this resistance may be avoided by using potent companion drugs [50, 59]. As the half-life of delamanid is 30–38 h, it is not necessary to stop delamanid long before other TB drugs, as it is for bedaquiline [59].

Short-term phase II clinical trial data have supported the use of delamanid against MDR-TB. A phase II RCT involving 481 MDR-TB patients showed that a delamanid-based regimen significantly increased the proportion of patients with sputum culture conversion at 2 months from 29.6% (placebo) to 45.4% (delamanid 100 mg

twice daily) and 41.9% (delamanid 200 mg twice daily) [60]. An open-label extension of this trial suggested that extending the use of delamanid from <2 to >6 months significantly promoted cure or treatment completion from 55% to 74.5% and significantly reduced mortality from 8.3% to 1.0% [61]. The available data about use of delamanid involve twice-daily dosing, which is inconvenient to supervise. Although the recommended delamanid treatment duration is 24 weeks, treatment extension has been done without noticeable safety issues.

Delamanid may be the novel drug of choice among HIV-infected patients when efavirenz is indicated, as evidenced by a phase I trial that showed no significant drug–drug interactions when co-administering delamanid with tenofovir, lopinavir/ritonavir or efavirenz [62]. It may also be the novel drug of choice for treatment of MDR-TB among children aged ⩾6 years and weighing >20 kg, except perhaps for MDR-TB involving the central nervous system, as delamanid is highly protein bound and protein binding may limit cerebrospinal fluid penetration, although data are lacking on this [63].

Delamanid is generally well tolerated. No dose adjustment is needed in mild to moderate renal impairment, although use in severe renal impairment is not recommended [62]. The main safety concern is QT interval prolongation, which may signify cardiotoxicity and possible sudden cardiac death. Delamanid significantly prolongs the QT interval from 3.8% (placebo arm) of patients to 9.9% (delamanid 100 mg twice daily) and 13.1% (delamanid 200 mg twice daily), but without associated clinical events [60]. QT interval prolongation becomes stabilised after slowly increasing in the first 6–10 weeks after drug use. Precautions should be taken when using delamanid with other QT interval-prolonging drugs, such as bedaquiline, clofazimine and fluoroquinolones (especially moxifloxacin). Despite the possible synergistic cardiotoxic effects, delamanid has been used increasingly with bedaquiline when treatment options are limited [64].

DM-6705 is a major delamanid metabolite closely correlated with QT interval prolongation [62], and its formation and metabolism are regulated by plasma albumin and CYP3A, respectively. Delamanid is therefore not recommended for patients with moderate to severe hepatic impairment and is contraindicated when serum albumin is <2.8 $g{\cdot}dL^{-1}$ or QTcF is >500 ms. Electrocardiography, serum albumin and electrolyte disturbance (especially hypokalaemia) should be checked at baseline and monitored as appropriate. Frequent monitoring of electrocardiography is indicated when serum albumin is <3.4 $g{\cdot}dL^{-1}$, a strong CYP3A inhibitor (such as lopinavir/ritonavir) is co-administered, or when QTcF exceeds 450 ms for males and 470 ms for females [62]. The WHO has provided national programmes guidance on the use of delamanid for treating MDR-TB [65].

Delamanid is being evaluated in a number of phase II or III MDR-TB drug trials, including NCT02583048, NCT01424670, NCT01859923, MDR-END and endTB [37].

Pretomanid

Like delamanid, pretomanid (also known as PA-824) is also a nitroimidazopyran (nitroimidazo-oxazine) and a pro-drug. Pretomanid requires intracellular activation by an F420-dependent glucose 6-phosphate dehydrogenase pathway. Pretomanid resistance is associated with mutations in the *fgd1* and *ddn* genes, which may account for the cross-resistance to delamanid [66–68].

 https://doi.org/10.1183/2312508X.10005616

Like isoniazid and delamanid, pretomanid kills aerobically by inhibiting cell wall mycolic acid biosynthesis [69]. Pretomanid also kills anaerobically, as its activation produces a desnitro metabolite that generates reactive nitrogen species (including nitric oxide), leading to depletion of intracellular ATP [66, 69, 70]. By consideration of the mechanism of actions, pretomanid is expected to show activity against both replicating and nonreplicating bacteria [71].

With an MIC of around 0.15–0.3 $mg{\cdot}L^{-1}$, pretomanid has demonstrated activity similar to a combination of isoniazid and rifampicin during the continuation phase in a murine drug model [68, 71, 72]. As pretomanid is highly protein bound, its activity in cavitary TB may be reduced [73].

The activity of pretomanid may be dependent on synergy with pyrazinamide, as evidenced by a phase II RCT of early bactericidal activity [74], which led to further evaluation of the combination of pretomanid, moxifloxacin and pyrazinamide in another phase II trial [75]. A phase II dose-ranging study suggested that it would be safe and efficacious to give pretomanid as 100–200 mg once daily [76], with no dose-limiting adverse events or clinically significant corrected QT changes. Thus, a phase III treatment-shortening trial (STAND) is evaluating a combination of moxifloxacin 400 mg once daily, pyrazinamide 1500 mg once daily and pretomanid (100 mg daily for 17 weeks, 200 mg daily for 17 weeks or 200 mg daily for 26 weeks) among drug-susceptible pulmonary TB patients, and concurrently evaluating a 6-month experimental regimen among pulmonary MDR-TB patients (table 1).

In addition to STAND, pretomanid is being evaluated in a number of phase II or III MDR-TB drug trials, which include NiX-TB, NC-005 and TB-PRACTECAL (table 1) [37].

Conclusions

The WHO has revised its MDR-TB treatment guidelines to recognise the roles of repurposed agents (linezolid and clofazimine) and approved novel drugs (bedaquiline and delamanid). A shorter (9–12 month) MDR-TB treatment regimen may benefit carefully selected patients with probable susceptibility to its components, especially fluoroquinolones and second-line injectable drugs. Phase II and III clinical trials are evaluating new regimens with different combinations of repurposed agents and novel drugs, with or without an optimal background regimen.

MDR- and XDR-TB are largely the result of human actions. Prevention of drug resistance is essential for curbing their progression [77, 78]. To sustain the benefits of new drugs and regimens, MDR- and XDR-TB are best managed by experienced clinicians, supported by reliable phenotypic and genotypic DST methods, including rapid molecular tests that can rapidly inform the clinician about initial drug choices to minimise the risk of amplifying drug resistance. An effective TB control programme plus a well-funded health infrastructure with an uninterrupted supply of quality drugs, a focus on special populations and infection control activities, and sufficient capacity for surveillance of drug resistance, is indispensable in the perennial war against TB.

To eliminate TB, science alone is insufficient [79]. It is imperative to concurrently address poverty and other socioeconomic issues that are associated with TB and its unfavourable outcomes.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10005616

Perspectives on antibiotic treatment of NTM pulmonary disease

Nicolas Schönfeld

Antibiotic treatment of pulmonary disease caused by NTM is based on a combination of antimycobacterial drugs. These drugs should be chosen according to the species involved. Evidence from prospective clinical trials is variable. *In vitro* susceptibility tests have not been validated, but are increasingly being recognised as a plausible potential aid to help combat diseases caused by difficult-to-treat NTM species, particularly in the case of treatment failure. In this chapter, the author seeks to explore areas of controversy and to challenge conventional thinking in the management of NTM pulmonary disease.

Cite as: Schönfeld N. Perspectives on antibiotic treatment of NTM pulmonary disease. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 245–252 [https://doi.org/10.1183/2312508X.10005716].

The pharmacotherapy for diseases caused by slowly growing NTM generally appears similar to the treatment of TB [1]. The simultaneous combination of specific antibiotics should kill the bacteria and prevent secondary resistance. However, the overall goal differs from the treatment of TB. In the field of NTM diseases, treatment most frequently achieves a lower bacterial load and thus a reduction of symptoms, but the likelihood of cure is hard to predict and the outcome often depends on the adherence of the patient, as well as the efficacy of the drugs [2, 3]. As NTM diseases regularly cause fewer symptoms compared with TB, the subjective benefit of treatment in view of the frequent and sometimes considerable side-effects is lower. Moreover, the overall morbidity of the patient may be dominated by an underlying disease, most often advanced COPD, with or without evidence of bronchiectasis.

Thus, in the author's view, it should always be understood that initiating a specific pharmacotherapy for NTM lung disease initially requires a diagnostic effort and a therapeutic concept of any underlying diseases in order to focus on the improvement of bronchial clearance [4]. To date, no study has reported on the efficacy of pharmacotherapy of NTM lung disease in patients without HIV infection in terms of the quality of

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pharmacotherapy of the underlying lung disease. Although such underlying diseases may influence the prognosis of the patient considerably, often more than the mycobacterial disease itself, reports in the literature almost exclusively focus on the variety of mycobacterial disease manifestations and on specific antimycobacterial pharmacotherapy.

Concrete recommendations about first-line treatment regimens for diseases caused by the most frequent NTM species have been published (in English) by the German Central Committee Against Tuberculosis and the German Respiratory Society [1]. In this chapter, the principles of pharmacotherapy will be considered in relation to NTM species that are difficult to treat, with an emphasis on MAC due to their frequent distribution among slowly growing NTM species worldwide.

Supported by long-term experience (particularly clinical and microbiological) in the author's institution, a preliminary note should address the permanent bone of contention of *in vitro* susceptibility testing [4]. The recoverability of NTM was highly controversial among US experts in the 1980s, resulting in the long-lasting predominant opinion that only in the case of failure of a calculated treatment of a disease caused by MAC, after 12 months of therapy, should such testing be carried out [5, 6]. At that time, an analogy to complicated TB had already been drawn. However, as we still rely, due to lack of an alternative, on plausible but more or less unvalidated *in vitro* susceptibility tests for the treatment of patients with MDR or even XDR *Mycobacterium tuberculosis* strains, should we not be willing to take such test results into consideration for reasons of mere plausibility when treating diseases caused by mycobacterial species such as MAC, *Mycobacterium malmoense* and other rarer species that are difficult to treat in general? The American Thoracic Society and Infectious Diseases Society of America have since become less reluctant to carry out *in vitro* tests at the start of therapy, which had previously probably been more due to practicability rather than evidence criteria or other disease-specific considerations [6]. On this point, the recommendations of the German Central Committee Against Tuberculosis and the German Respiratory Society are more open minded, with an acknowledgement that the treatment of any mycobacterial disease is still based on common clinical and microbiological experience, and not on the comparatively little evidence of prospective studies and their previously mentioned limitations [1]. Methodological considerations and limitations should always be kept in mind when interpreting the results [7]. However, two recent, although statistically weak, studies for the purpose of approval of novel drugs for the treatment of MDR strains of *M. tuberculosis* show that this approach is currently accepted, possibly as an act of necessity [8, 9]. Therefore, laboratories with the available resources should be encouraged to carry out testing at initial detection of MAC and other difficult-to-treat mycobacterial species with a clinically identified need for treatment.

Conventional compounds

Rifamycins are, as for TB, considered to form the backbone of a combined regimen against MAC and most of the other slowly growing NTM species, whether they appear to be simple or difficult to treat. Rifabutin has more favourable MICs *in vitro* than rifampicin and so this newer derivative formed part of the treatment recommendations for MAC for several years after its approval [5]. However, the side-effects of rifabutin, especially when used in a triple regimen with clarithromycin and ethambutol, were recognised to be high. As MICs for all rifamycins are expected to be similar, rifampicin is currently recommended

 https://doi.org/10.1183/2312508X.10005716

as the rifamycin component in the triple regimen [5]. The long-term toxicity of rifampicin seems to be low, with a focus on neutropenia, and the recommended dose is 10 $mg \cdot kg^{-1}$ body weight with a maximum of 600 mg once daily, as for the treatment of TB [1]. If it is decided that a strain from a patient should be tested for drug susceptibility *in vitro*, closer supervision of treatment success should be provided if the critical concentration of 0.5 $mg \cdot L^{-1}$ for rifabutin fails to inhibit growth [10]. Testing MAC for rifampicin susceptibility *in vitro* regularly indicates resistance according to the criteria for *M. tuberculosis*, with a critical concentration of 1 $mg \cdot L^{-1}$ [7]. Nevertheless, it is a common doctrine for this drug to be a component of a first-line treatment combination for MAC, despite these *in vitro* results. Rifamycins have never been tested prospectively against other drugs, but clinical experience speaks in their favour [1, 6].

In the author's view, it is more difficult to judge ethambutol and the questionable tradition of its clinical efficacy in MAC infections, in spite of unfavourable *in vitro* data. A dogma-like element of each institutional treatment recommendation in the last three decades has been to include this bacteriostatic drug (approved in 1961) as part of combination therapy for diseases caused by MAC and other difficult-to-treat NTM species. In 1968, the use of ethambutol was propagated by the National Tuberculosis and Respiratory Diseases Association in the USA, despite no clinical results being available at that time [11, 12]. *In vitro* susceptibility testing to determine the critical concentration, as for the testing of *M. tuberculosis* strains, invariably revealed resistance to this drug. The results for ethambutol compared with other substances are highly dependent on the culture method; therefore, testing was generally considered unreliable for MAC strains. However, in a study with just 12 AIDS patients given a daily monotherapy of only 800 mg ethambutol, strains from the group of patients with treatment failure as well as those with treatment success showed the same MICs [13]. From these variable data, it was concluded that there was no correlation between *in vivo* and *in vitro* results for the treatment of MAC (and other species) with this compound [13]. Other working groups showed higher MICs *in vitro* for MAC than for other mycobacterial species, but also a synergism with other antimycobacterial drugs [14, 15]. It was concluded that there must be a certain clinical efficacy in combination therapy and there was speculation about the value or need for a higher daily single dose. These speculations led to the general recommendation of an initial triple therapy including daily ethambutol at 25 $mg \cdot kg^{-1}$ body weight [5]. Later recommendations for an intermittent treatment with such a high single dose were published without any data basis [6].

It is difficult to draw more reliable conclusions on ethambutol after decades of clinical use as part of a combined induction treatment for infections caused by MAC. The drug seems to have proved its worth in practice. From the scientific point of view, a general recommendation for treatment without *in vitro* testing appears weak, relying merely on tests without prospective comparative studies. In the author's view, the determination of MICs could support clinical decisions in cases of treatment failure. Would such an approach be more plausible than recommending the drug without further means for treatment? This question seems worthy of discussion, but so far no scientific society has come up with such a suggestion.

The recommendation to include clarithromycin in a combined treatment regimen is much clearer. *In vitro* studies on susceptibility as well as monotherapeutic clinical data suggest a therapeutic benefit. The intracellular accumulation rate is very high, a favourable quality for any antimycobacterial drug for the long-term treatment phase [16]. Furthermore, the

intracellular accumulation compensates for the lower AUC when given in combination with rifamycins. Clarithromycin is known to induce secondary resistance, at least during single-drug treatment [17]; therefore, *in vitro* susceptibility tests appear to be reasonable, particularly in cases of treatment failure. It is unknown whether differences between the MICs for *Mycobacterium avium* and *Mycobacterium intracellulare* are clinically relevant; the MICs for *M. avium* seem to be more unfavourable [18]. However, the standard dose of 500 mg twice daily is uncontroversial. Although azithromycin also has favourable pharmacological properties, the long-term treatment experience with clarithromycin over ~20 years has provided reassurance about the safety of this drug when given for ⩾1 year.

Moxifloxacin has *in vitro* and *in vivo* activity against MAC in experimental models, and has been shown to contribute favourably in a combined treatment regimen [19]. Due to its safety in long-term treatment regimens for MDR-TB, the author proposes that this drug should now be considered a first-line drug in the treatment of MAC or other species that are difficult to treat and have been shown to be susceptible, as expressed by low MICs (*e.g.* 0.5 or 1.0 $mg{\cdot}L^{-1}$) [20].

Conventional (hydrophilic) amikacin is likely to be an effective drug to treat diseases caused by MAC [21]. However, from the author's experience, its toxicity and the intravenous route of administration limit the use of this drug to individual and exceptionally severe situations.

Isoniazid is not recommended for the treatment of MAC, but it is used in regular doses (3–5 $mg{\cdot}kg^{-1}$ body weight) for species that are easy to treat, such as *Mycobacterium kansasii* (table 1). However, MICs *in vitro* vary for different strains of this common species and on average are ~1 $mg{\cdot}L^{-1}$, and thus higher than the breakpoint concentration for *M. tuberculosis* of 0.25 $mg{\cdot}L^{-1}$ [23]. It is believed that this drug is effective as a partner in a combined regimen, but this is only on the basis of pharmacological plausibility. This recommendation is currently upheld, but may be influenced in the future by discussions about the required daily dose to treat "low-level" resistant strains of *M. tuberculosis* [24].

Table 1. A clinical classification system for NTM, as originally proposed by William Bailey in 1983 [22] and modified by the author

Easy to treat[#]	**Difficult to treat**[¶]	
	A	**B**
Mycobacterium kansasii	MAC	*Mycobacterium abscessus*
Mycobacterium xenopi	*Mycobacterium scrofulaceum*	*Mycobacterium chelonae*
Mycobacterium szulgai	*Mycobacterium simiae*	*Mycobacterium fortuitum*
Mycobacterium marinum		*Mycobacterium ulcerans*

[#]: easy to treat with standard antimycobacterial therapy including isoniazid, rifampicin and ethambutol but not pyrazinamide (prototype *M. kansasii*); [¶]: difficult to treat, nonstandard antimycobacterial therapy required and further divided into subcategories A and B: those in subcategory A appear to be quite comparable in terms of their drug response to MAC, while those in subcategory B are rapidly growing pathogens that seem to respond to some of the standard and/or other antibiotics. Information from [22].

 https://doi.org/10.1183/2312508X.10005716

Investigational or alternative drugs

A sustained-release lipid formulation of amikacin for inhalation may offer a new effective component in a combination treatment regimen for MAC. However, in a recently published study on the daily inhalation of amikacin 590 mg *versus* placebo, the primary end-point, *i.e.* a change from baseline to day 84 on a semiquantitative mycobacterial growth scale, was not reached [25]. Interestingly, an acquired mutational resistance to amikacin was detected in single cases, with MICs $\geqslant$64 mg·L^{-1}, a fact that once again advocates for the use of *in vitro* susceptibility tests, and even repeated tests, for MAC, as it is likely that such resistance contributes to treatment failure. Efficacy of liposomal amikacin for the majority of clinical strains can nevertheless be expected; studies are currently pending to determine the optimal dosage and effectiveness. The optimal combination partners also need to be determined, especially in terms of synergy, as shown for clofazimine [26]. One obstacle to the use of liposomal amikacin, at least in patients without advanced cystic fibrosis or AIDS, could turn out to be a high price at the time of entry to the market, considering the relatively low burden of symptoms.

Clofazimine, which is used in combination with rifampicin and dapsone for the treatment of disease caused by *Mycobacterium leprae*, also seems to be effective in the treatment of MAC disease [27]. Using a single daily dose of 100 mg, long-term toxicity is mild and usually tolerable.

Linezolid has shown MICs $\geqslant$16 mg·L^{-1} for the majority of MAC strains and is thus considered resistant from a microbiological point of view [28]. Clinical data do not exist, but in view of the high accumulation rate of the lipophilic compound, discussion on the use of this drug should remain open [29]. Novel oxazolidinone analogues may eventually contribute new options for the treatment of MAC disease [30].

Whereas moxifloxacin targets gyrase A, a novel aminobenzimidazole has recently been developed, VXc-486, that targets gyrase B and inhibits the growth of MAC strains at favourable concentrations (MICs of 0.1–2.0 mg·L^{-1}) [31].

Last but not least, our working group has tested delamanid, a novel agent derived from the nitro-dihydro-imidazooxazole class of compounds, which inhibits mycolic acid synthesis and has been approved for the treatment of MDR-TB. It is characterised pharmacologically by an excellent intracellular bactericidal activity and high accumulation rate [32]. MAC strains, including single strains with high MICs against clarithromycin, exhibited low MICs against delamanid, varying from 0.013 to 0.4 mg·L^{-1} [33]. The MICs tend to be only slightly higher than those published for strains of *M. tuberculosis*. Thus, delamanid appears to be interesting for the oral treatment of severe or relapsing MAC diseases.

Rapidly growing mycobacteria

Mycobacterium abscessus, together with *Mycobacterium chelonae* and *Mycobacterium fortuitum*, are the clinically most relevant rapidly growing NTM species for pulmonary disease. All are difficult to treat pharmacologically and the principles of pharmacotherapy should be clearly explained for *M. abscessus*, which is one of the most frequently isolated species of mycobacteria in patients with cystic fibrosis [34].

Combination therapy of oral clarithromycin and parenteral administration of amikacin plus cefoxitin or imipenem for ~2–4 months, followed by 6–12 months of oral therapy with sensitive tested drugs, promises improvement but often no definitive cure [6]. It should be noted that the mycobacteria growth indicator tube (MGIT) method cannot currently be used for susceptibility testing of rapidly growing species; liquid medium-based methods with manual evaluation are used for certain circumstances [1]. The interesting observation that *M. abscessus* strains start to grow with a prolonged incubation time in the presence of clarithromycin, as well as the genetic detection of a gene involved, led to the conclusion that certain *M. abscessus* strains possess an inducible clarithromycin resistance [35, 36]. Findings such as these again indicate that *in vitro* susceptibility testing should be considered for inclusion in a therapeutic concept for individual patients, despite the methodological limitations.

Among the macrolides, azithromycin may have a better efficacy than clarithromycin [37]. Moxifloxacin is also effective, but an antagonistic effect was observed when used in combination with macrolides [38]. A study in Taiwan found the following sensitivities *in vitro* among 40 isolates: 95.0% for amikacin, 32.5% for cefoxitin, 10.0% for ciprofloxacin, 92.5% for clarithromycin, 7.5% for doxycycline, 12.5% imipenem, 22.5% for moxifloxacin, 7.5% for sulfamethoxazole and 100% for tigecycline [39]. However, the authors of the study still observed treatment failure in 27.3% of patients after 12 months of a combination therapy with clarithromycin, amikacin and a third antibiotic. It is remarkable that no cephalosporin other than cefoxitin shows susceptibility *in vitro*. In diseases caused by certain strains of *M. abscessus* subsp. *bolletii* (previously described as *Mycobacterium massiliense*), the response to therapy with macrolides seems to be better, because the development of resistance has been observed less frequently [37].

Innovative substances to treat pulmonary diseases caused by *M. abscessus* could be bedaquiline [40] or inhaled liposomal amikacin [25], but further research is needed to test their clinical efficacy in accordance with *in vitro* data.

Conclusions

Bailey [22] originally proposed the classification of NTM into three classes: 1) nonpathogens (prototype *Mycobacterium gordonae*), 2) those that are easy to treat with standard antimycobacterial therapy (corresponding to an anti-TB treatment without pyrazinamide) and 3) those that are difficult to treat with standard antimycobacterial therapy and require other approaches (table 1). Detailed information on distinct species has been reviewed elsewhere [1]. Beyond general recommendations, especially for patients with diseases caused by difficult-to-treat mycobacteria, the author would like to encourage treating physicians to make use of any information available in cases of treatment failure, including *in vitro* susceptibility tests and promising laboratory data about newer or newly interpreted compounds. Such alternative treatment concepts should ideally be designed and followed in an interdisciplinary setting, working with specialised pneumologists, infectious disease specialists and microbiologists.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10005716

Antibiotics for pleural infections

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Pleural infection remains a common and serious respiratory condition with important implications for patients and healthcare services. Diagnosis of the condition can be challenging and its management may require a multidisciplinary approach. Antibiotic therapy, along with pleural drainage, forms the cornerstone of treatment for pleural infection. Culture-positive samples (including both pleural fluid and blood) are found in ~60% of patients and correct empirical therapy is of paramount importance. Evidence from RCT and case series data have shown that the combination of an intrapleural tissue plasminogen activator and DNase therapy can potentially improve outcomes, but further research is needed to establish the first-line use of such agents. In this chapter, we cover the management of pleural infections, including medical treatment, the role of intrapleural agents and surgical treatment, with a focus on the use of antibiotics.

Cite as: Bhatnagar R, Skouras VS, Rahman NM, *et al.* Antibiotics for pleural infections. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 253–263 [https://doi.org/10.1183/2312508X.10005816].

Pleural infection is a common clinical condition faced by respiratory physicians, thoracic surgeons and internal medicine physicians, with an annual incidence of approximately 80 000 new cases in the USA and UK combined [1]. The importance of the disease is founded not only on its high morbidity and mortality but also on the fact that its diagnosis can be challenging and its management often requires a complex multidisciplinary approach [1–5].

Little changed between the first description of the management of pleural infection in 500 BC by Hippocrates and the Empyema Commission during World War I. During this time, open surgical drainage was relied on as the default treatment, despite this causing an unacceptably high mortality of up to 70% [1, 6]. However, significant progress has since been made, with advances including the use of closed chest tubes to drain infected pleural fluid, the development of newer surgical techniques that allow pleural debridement without open thoracotomy (*i.e.* video-assisted thoracoscopic surgery (VATS)), the administration of intrapleural fibrinolytics to facilitate pleural fluid drainage and, perhaps most importantly,

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the discovery of antibiotics [1, 5, 7]. The aim of this chapter is to provide a concise overview of the spectrum of pleural infections and to describe recent advances in its management, with a special focus on the use of antibiotics.

Epidemiology

The incidence of pleural infection appears to be increasing worldwide, with a rate that is age dependent (higher in children and adolescents) and is increasing by as much as 2.8% per year [1, 8, 9]. The cause of this increasing incidence in children is unclear, but it is probably related to the widespread introduction of childhood vaccinations (*e.g.* pneumococcal conjugate vaccine), which has changed the flora seen in routine infections in children. In general, the disease is more common in the paediatric and elderly populations, and males are affected twice as often as females [4, 5, 8–11]. Pleural infection is also more frequent in patients with diabetes mellitus, rheumatoid arthritis, chronic lung disease or immunosuppression, as well as in individuals with a history of alcoholism or intravenous (*i.v.*) drug abuse [1, 2, 12]. Poor dental hygiene and factors predisposing to aspiration (such as gastro-oesophageal reflux, seizures and the use of alcohol or sedatives) have also been associated with an increased incidence of anaerobic pleural infections [3, 13]. The most common precursor to frank pleural infection by far is parapneumonic effusion, which is detectable in up to 70% of cases [13]. Less frequent causes include chest trauma, abdominal infections, bacteraemia, oesophageal perforation and chest tube insertion, whereas no underlying aetiology is found in up to one-third of cases [3, 13]. Although the overall mortality from pleural infection is ∼20%, it rises to >30% in susceptible populations, such as those already mentioned [4, 5, 14, 15].

Clinical and radiological diagnosis

The diagnosis of pleural infection often rests on there being an appropriate degree of clinical suspicion. In the majority of cases, it is a complication of an underlying pneumonia, but it may also be the primary presentation of the disease [1]. A patient with pneumonia who does not exhibit the expected level of improvement, in the presence of a pleural effusion, should have the diagnosis sought and ruled out [1]. In most cases, the presence of a moderate or large pleural effusion can easily be identified on a posteroanterior and/or lateral chest radiograph [16]. In patients with pneumonia, however, a chest radiograph misses ∼15% of parapneumonic effusions, especially in patients with lower lobe consolidation [17]. Thoracic ultrasound is more sensitive in detecting pleural fluid, can guide pleural interventions, and also carries a benefit in the context of small and multiloculated collections [1, 18, 19]. CT scanning of the chest is now also viewed as a standard procedure in suspected pleural infection, as it is more likely to be able to delineate the overall pattern of loculation, as well as identify a potential source [1, 20].

Although pleural fluid sampling is almost always necessary to demonstrate that a pleural effusion is infected (by aspiration of pus, isolation of bacteria from the pleural fluid or the finding of a pleural fluid pH <7.20), radiology may also provide information that excludes or suggests the diagnosis of pleural infection. For example, small pleural collections of <10 mm depth on chest ultrasound, CT or decubitus radiograph are typically not infected and do not require sampling [16, 21]. In contrast, the detection of loculations with the use of any imaging modality, the presence of homogeneously echogenic fluid on ultrasound, or

 https://doi.org/10.1183/2312508X.10005816

the presence of pleural thickening, pleural enhancement or extrapleural fat attenuation on contrast-enhanced chest CT are suggestive of the presence of frank infection in the pleural cavity [1, 22–26].

Microbiology

There is increasing recognition that the microbiology of pleural infection is distinct from that of pneumonia and that its presentation can vary dramatically according to a number of factors, including time course, clinical setting and origin, patient age, and underlying immunocompetence [1, 2, 4, 27]. The relative frequency of various bacteria among pleural fluid isolates has varied over time, with a predominance of *Streptococcus pneumoniae* (60–70% of cases) in the pre-antibiotic era being followed by the increasing isolation of *Streptococcus pyogenes*, *Staphylococcus aureus* and anaerobes after the advent of antibiotics [28]. Cumulative data from contemporary studies show that pleural infection is now most commonly (60% of cases) caused by aerobic Gram-positive organisms, usually streptococci (*Streptococcus milleri* in adults and *S. pneumoniae* in children), followed by *S. aureus* [29]. Aerobic Gram-negative (*i.e. Haemophilus influenzae*, *Escherichia coli*, *Pseudomonas* spp. and *Klebsiella pneumoniae*) and anaerobic (*i.e. Peptostreptococcus*, *Fusobacterium*, *Bacteroides* and *Prevotella* spp.) organisms are also common isolates (15% and 14%, respectively), with the former being cultured most commonly from patients with comorbidities, and the latter usually being associated with polymicrobial infections and patients with poor dental hygiene or aspiration pneumonia [2, 29]. Although fungal pleural infection is extremely rare (<1% of cases) in immunocompetent individuals, *Candida* spp. have been isolated from the pleural fluid of immunosuppressed patients [30]. Following analysis of the First Multicenter Intrapleural Sepsis Trial (MIST1), which is the largest RCT on pleural infection (n=434) to date, it was shown that community- and hospital-acquired pleural infections should perhaps be viewed as two distinct clinical entities due to the significant differences not only in their prognosis (1-year mortality of 17% *versus* 47%, respectively) but also in their microbiology [2]. Streptococci, including *S. milleri* (32%), *S. pneumoniae* (13%) and other streptococcal species (7%), were the most common isolates in the community, followed by anaerobes (16%) and staphylococci (11%). In contrast, the most frequent isolates in hospital were staphylococci (46%), two-thirds of which were methicillin resistant, and aerobic Gram-negative organisms, including *Enterobacteriaceae* (16%), enterococci (13%) and *Pseudomonas* spp. (5%).

General management of pleural infection

The management of a patient with pleural infection usually requires a multifaceted approach, with a clear understanding of the probable causative organisms playing a major role. Although antibiotic therapy forms the cornerstone of treatment, in a significant number of patients it cannot be relied on alone to both cure a patient of acute pleural sepsis and ensure the best long-term outcomes. The best strategies often employ antibiotics in conjunction with nutritional support, chest drain insertion and occasionally surgical approaches. It should be noted that, in some cases, such as in patients who are not suitable for intervention or in those who refuse invasive therapies, isolated antibiotic therapy may be necessary. In other patients, primarily due to the increasingly routine use of both CT and bedside thoracic ultrasound, it has become common to identify small (and often complicated) pockets of intrapleural fluid in association with primary lung parenchymal infection. There may be an argument for treating both of these patient groups without an

invasive approach, perhaps prioritising long-term outpatient antimicrobial treatment with careful monitoring for sepsis.

In the presence of sepsis and a pleural collection with evidence of complexity, however, the standard approach requires the insertion of an intercostal drainage tube to evacuate the inflammatory thoracic contents [1]. The ideal size of chest drain and the technique used to insert it continue to be debated. There is evidence to suggest that, in some settings (*e.g.* malignant pleural effusion), larger drain sizes can be more effective, albeit at the cost of increased discomfort to the patient [31]. The suggestion that smaller-bore tubes impede free drainage of viscous, empyematous fluid may be countered by the use of regular intrapleural saline flushes, although this practice is not always achievable in reality, despite being recommended in national guidelines [1]. Extrapolating from this, formal saline irrigation of the pleural space has been shown to improve drain output and reduce the need for surgical referral in a randomised pilot study [32], with this practice considered routine in some European centres.

For patients with chest drains and persistent pleural sepsis, treatment with intrapleural fibrinolytic therapy has long been viewed as an attractive option, primarily as a mechanism to avoid extended hospital stays or the need for referral for surgery and its associated risks. The MIST1 trial examined the use of intrapleural streptokinase as a solitary agent, showing that there was no benefit in any clinically relevant outcome using this approach [4]. The follow-up trial, MIST2, confirmed this finding but demonstrated that benefits could be achieved with the use of an alternative intrapleural fibrinolytic (tissue plasminogen activator) in combination with DNase [5]. Observational data seem to be in agreement that tissue plasminogen activator/DNase can be used safely in routine practice, although the exact role in treatment pathways has not yet been clarified [33].

A few centres in Europe have advocated the use of medical thoracoscopy in "early" empyema to interrupt pleural adhesions and facilitate complete drainage of the fluid by transforming a multiloculated pleural cavity to a unified space. The available studies are all case series; however, despite showing good results, these findings have not been confirmed with RCTs [34, 35]. Such studies are required to probe the overall role of medical thoracoscopy in pleural infection, especially with regard to setting a more defined limit for "early" intervention, which is challenging due to highly variable progression among patients.

In the event of the above ("medical") treatment failing to work, it is recommended that patients be referred for consideration for surgical therapy [1], although the threshold for when to make this decision is subject to a degree of institutional variability and may be influenced by other factors, such as the degree of septicaemia or appearances on thoracic imaging. For many years, the default approach to surgical clearance of the pleural space following pneumonic or primary pleural infection was open thoracotomy and debridement. However, the use of VATS has now become the norm for all but the most challenging of cases. By refining this method, morbidity, mortality and recovery times in this setting have become negligible in many centres [36].

Choosing the right antibiotic in pleural infection

As with almost any other infection, the degree of illness or sepsis with which a patient can present is affected by a wide range of factors, including the patient's immune status and the

 https://doi.org/10.1183/2312508X.10005816

likely source and resistance profile of any implicated microbes. Rapid, empirical antibiotic therapy forms the mainstay of most suspected pleural infection cases, as it is usually impractical to wait for accurate microbiological results (from blood or pleural fluid, the former only yielding results in ~10% of cases [4]) during the early stages of an acute presentation. Gram staining and culture testing of fluid taken using traditional collection techniques tend to be unhelpful in identifying causative organisms [4]. However, it has been shown that, by using blood culture bottles, the positive yield from microbiological testing can be increased by a clinically significant margin (~40–60%), suggesting that this should be routine practice [37]. The novel approach of quantified nucleic acid amplification techniques may have the potential to dramatically alter the wider understanding of the pleural infection microbiome [38], although as yet it is unable to give clinically useful information regarding sensitivities.

In the absence of direct guidance by positive samples, the choice of empirical antibiotics should be determined by an understanding of the probable causative organism in the patient's particular geographical and clinical situation [1, 38]. This information is often codified in local hospital guidelines (table 1). Although practice varies markedly throughout Europe, for community-acquired infection, empirical treatment might include a β-lactamase inhibitor-containing drug (such as amoxicillin–clavulanate or piperacillin–tazobactam), third-generation cephalosporins or quinolones, or broad-spectrum antipseudomonal penicillins such as piperacillin. In hospital-acquired infections, antibiotics should cover Gram-negative organisms (with piperacillin–tazobactam, quinolones, carbapenems or cephalosporins) and MRSA (with vancomycin, clindamycin or linezolid). In both situations, advice is generally given to ensure that anaerobic coverage is also provided, as the pleural space offers an ideal breeding ground for such organisms [39]. As pleural infection due to *Legionella* spp. or *Mycoplasma pneumoniae* is rare, the use of macrolides is not routinely recommended; these are added only in confirmed or strongly suspected cases [1]. Regardless of the initial choice of antibiotic, early sampling and analysis of blood and pleural fluid should always be undertaken to allow later adjustment of treatment as required [1].

There is no clear evidence for the optimum length of treatment, but a prolonged course (⩾3 weeks) is usually recommended [1]. For the most part, the *i.v.* route is preferred initially; however, in those patients in whom invasive drainage is not an option, or in those in whom it is not felt to be necessary, extended courses of oral antibiotic therapy alone may be required. In such cases, early and frequent review in the outpatient setting is generally prudent to ensure there is no evidence of relapse.

Antibiotics and the pleural space

Lode *et al.* [40] summed up the behaviour of the pleural cavity with regard to antibiotics as "a partial extracellular, extravascular compartment in which the concentration course probably correlates more to the interstitial lung concentrations than to that of the sputum". There has always been a logical attraction to administering antibiotics directly into the pleural cavity in cases of infection, although the weight of current evidence would suggest that, in the typical medical patient, this has no advantage over more common (and more accessible) methods [41–43]. In addition, the overall quality of evidence regarding this question is poor, meaning that the American College of Chest Physicians guidelines state that the review panel was unable to make a recommendation regarding their use due to

Table 1. List of common organisms

Aerobic/ anaerobic	Bacterial group and common causes of pleural infection	Potentially suitable antibiotics with good pleural penetration	Notes
Aerobes	Streptococci: *Streptococcus milleri*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, enterococci	Penicillins, cephalosporins, third- or fourth-generation quinolones, clindamycin, β-lactamase inhibitor combinations, carbapenems	Avoid aminoglycosides; macrolides generally not recommended; enterococci covered only by penicillins, β-lactamase inhibitor combinations and carbapenems (excluding ertapenem)
	Staphylococci: *Staphylococcus aureus*, MRSA, *Staphylococcus epidermidis*	Cephalosporins, third- or fourth-generation quinolones, clindamycin, β-lactamase inhibitor combinations, carbapenems	Macrolides generally not recommended
	Gram-negatives: *Escherichia coli*, *Proteus* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*	Third- or fourth-generation quinolones, cephalosporins, carbapenems, β-lactamase inhibitor combinations	*P. aeruginosa* not covered by amoxicillin–clavulanate or ertapenem
Anaerobes	*Fusobacterium* spp., *Bacteroides* spp.	Metronidazole, carbapenems, β-lactamase inhibitor combinations, clindamycin, third- or fourth-generation quinolones	Ensure anaerobic coverage is included in any empirical treatment regimen

Information from [2].

insufficient data [13], while the British Thoracic Society recommend against their use in routine practice altogether [1].

The first report of the use of penicillin as an intrapleural therapy for TB and empyema came within only a few years after its discovery and commercialisation [44]. This was followed in the next decade by similar descriptions of the use of erythromycin [45] and amphotericin B [46] in bacterial and fungal empyema, respectively. Up to and including the 1990s, the majority of publications pertaining to antimicrobials in the pleural space were descriptions of absorption patterns and drug concentrations found in various types of pleural fluid following parenteral or oral administration [41, 42, 47–52]. Tests and comments have been made regarding a variety of antimicrobial families, including first-, second- and third-generation cephalosporins [41, 42, 48–50, 53–61], penicillins [44, 62–66], quinolones [43, 67–76], aminoglycosides [51, 52, 77, 78], and carbapenems [79, 80], as well as antituberculous agents [44, 76, 81–83] and antifungals [46, 84–86]. In general, these investigations were able to reveal that the MIC for most respiratory pathogens was readily achievable in the pleural space with little need for invasive pleural procedures to specifically

 https://doi.org/10.1183/2312508X.10005816

administer the agents [41, 47, 58, 59, 87–89]. This appears to be in spite of the fluid/serum concentration ratio often being found to be relatively low (*e.g.* only 15% with vancomycin) [90]. The excretion of antimicrobials from the cavity has also been noted to be dramatically slower than that seen in other tissues, with clearance of some drugs perhaps being affected by other factors, such as renal function [49], serum protein binding [56] and volume of fluid [78].

The degree of pleural inflammation, pus formation or thickening evident may also alter the absorption and effectiveness of a drug *in vivo* [39]. Using a novel rabbit model of the pleural space, Teixeira *et al.* [91] postulated the following hierarchy for the pleural penetrance of a series of common antibiotics following *i.v.* administration: penicillin>metronidazole> ceftriaxone>clindamycin>vancomycin>gentamicin. In terms of general effectiveness, drugs that combine antibiotics with secondary enzyme inhibitors (*e.g.* clavulanic acid, tazobactam and cilastatin) may well have an advantage over standard agents, as they appear more resistant to the inhibitory effects of local pleural inflammation [39], especially that caused by more adaptive organisms, such as *Pseudomonas aeruginosa* [92].

There are some major exceptions to these patterns, however, with the first appearing to relate to antituberculous medications. A number of authors have postulated that there is a greater chance of developing drug-resistant pleural TB if treatment is based only on antituberculous medications, due to the variable penetration leading to potentially inadequate therapy [81, 82]. In general, these authors showed the achievable concentrations of rifampicin and pyrazinamide to be below the desired level, whereas isoniazid appeared to be readily absorbed into the pleural cavity [81, 82]. However, one small randomised series was unable to show any meaningful benefit in early complete drainage of TB effusions other than short-term relief of dyspnoea, although this study was not designed to look for the incidence of drug resistance or antibiotic penetrance levels [93]. A further note of caution relates to the use of aminoglycosides in the pleural space, as they appear to be readily inactivated in the presence of empyematous or inflammatory fluid, potentially leading to inadequate MICs [52, 87, 88]. This is despite other studies showing that direct pleural injection can still lead to toxic systemic side-effects, such as ototoxicity [94].

The question of whether or not to instil antibiotics directly into the pleural cavity has been tested more robustly in the surgical setting than in the treatment of patients with primary or parapneumonic pleural infection, perhaps because of the relative ease with which large volumes of intrapleural medication can be administered either during the operation or immediately post-operatively. There have also been more descriptions of the use of pre-operative prophylactic antibiotic doses to prevent subsequent pleural infection in the surgical setting [70, 79, 95, 96], although the most comprehensive review in this area actually related to their use following chest trauma requiring intercostal tube insertion, with the authors undertaking a systematic review of more than 1200 patients and concluding that prophylactic antibiotics are of benefit in reducing infective complications, including empyema [97]. Based on current evidence, the use of prophylactic antibiotics for routine chest drain insertion is not recommended.

In general, ensuring and maintaining sterility of the pleural space after thoracic surgery is of paramount importance, especially in the context of more involved procedures, such as pneumonectomy. In such cases, the development of empyema carries with it the risk of persistent bronchopleural fistula, which may represent a life-threatening complication [98]. Nonetheless, the quality of evidence for intrapleural antibiotics remains somewhat limited,

with most reports consisting of retrospective case series, once again relating to a wide range of antibiotic agents [95, 96, 99–101]. Those series that have reported benefits from this practice have suggested improvements with regard to length of stay [99], lack of early recurrence in those already diagnosed with empyema [100] and reduced development of empyema in those undergoing routine surgery. The last effect was demonstrated in one retrospective review of more than 90 pneumonectomy cases, in which those patients who underwent a pleural antibiotic wash in addition to pre-operative *i.v.* antibiotics appeared to have fewer local infective sequelae [96]. A similar finding was reported by Baltayiannis *et al.* [95], who used an intrapleural fusidic acid wash to complement *i.v.* antibiotics in the latter half of a series consisting of 492 thoracotomy patients.

Conclusions

Antibiotic therapy, along with pleural drainage, forms the cornerstone of treatment for pleural infection. In patients demonstrating evidence of pleural sepsis, empirical antibiotics should be started in advance of any culture results being available. Selection of medication should be adapted to both local microbiological patterns and probable causative organism based on the presenting history, and should normally include anaerobic cover. Apart from aminoglycosides and certain antituberculous drugs, antibiotic penetration into the pleural fluid and tissues following *i.v.* or oral administration is generally excellent, meaning that there is little or no role currently for routine intrapleural antibiotic instillation.

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Disclosures: I. Psallidas has received a RESPIRE2 European Respiratory Society Fellowship (RESPIRE2-2015-7160).

Chapter 16

Antibiotics in interstitial lung diseases

Davide Biondini and Paolo Spagnolo

Interstitial lung diseases (ILDs) represent a large and heterogeneous group of disorders characterised by varying degrees of inflammation and fibrosis. Idiopathic pulmonary fibrosis (IPF), the most common form of ILD, is a relentlessly progressive and invariably fatal disease, which is thought to result from a complex interaction between host/genetic and environmental factors. In IPF, a potential role for infection in disease pathogenesis and progression or as a trigger of disease exacerbation has long been postulated, but studies based on traditional culture methods have yielded inconsistent results. Accordingly, few studies have investigated the efficacy of antibiotics in this setting. The application of new culture-independent techniques for microbiological analysis in IPF has revealed previously unappreciated alterations of the lung microbiome in these patients. The application of these methodologies to larger populations of carefully characterised patients will hopefully clarify the role played by the lung microbiome in IPF, leading to the development of novel treatments for this fatal disease.

Cite as: Biondini D, Spagnolo P. Antibiotics in interstitial lung diseases. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 264–275 [https://doi.org/10.1183/2312508X.10005916].

The interstitial lung diseases (ILDs), also referred to as diffuse parenchymal lung diseases, represent a large and heterogeneous group of conditions that are classified together because of similar clinical, physiological, radiological and histological manifestations [1]. The term "interstitial" is, however, somewhat misleading in that ILDs often also affect the airways, lung parenchyma, blood vessels and pleura. In the last two decades, our knowledge on ILDs has improved greatly. New insights into disease pathogenesis along with the widespread use of high-resolution CT scanning have contributed significantly to a better understanding of these uncommon disorders, which remain a challenge to even the most experienced clinicians, radiologists and pathologists. Indeed, the ILDs embrace over 200 entities of known and unknown origin, with or without associated systemic diseases, of acute or chronic onset, of varying and often unpredictable degrees of progression, and with highly variable responses to treatment [2].

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Idiopathic pulmonary fibrosis (IPF), the most common and severe of the idiopathic interstitial pneumonias (IIPs), is an inexorably progressive and invariably fatal disease with a life expectancy worse than that of many cancers [3]. The incidence and prevalence of the disease increase with each decade of life, with the mean age at diagnosis being ~65 years of age. The pathobiology of IPF is poorly understood; however, the disease is believed to result from abnormal wound-healing mechanisms following repetitive alveolar damage [4]. The probable importance of recurrent injury as a contributor to the initiation of the disease is also suggested by the heterogeneity (both spatial and temporal) observed in usual interstitial pneumonia (the histological correlate of IPF) [3]. This pathogenic paradigm implies that environmental and host/genetic factors are probable contributors to the development of IPF. While the exact trigger for the fibrotic response of IPF remains unknown, infectious agents, including both viruses and bacteria, have the potential to cause alveolar epithelial cell injury and apoptosis, and the capacity to modulate the host response to injury [5]. In addition, a mutant *MUC5B* gene, which encodes a mucin required for a normal macrophage function and effective mucociliary clearance of bacteria in mice [6], is associated with an increased risk of developing IPF [7], suggesting that infection may act as a cofactor in fibrosis initiation in genetically predisposed individuals. In this regard, it has also been reported that IPF patients display activated leukocyte populations and increased expression of host defence genes [8]. Moreover, active infection in IPF carries a high morbidity and mortality [9], whereas immunosuppression (*e.g.* resulting from a combination of prednisone, azathioprine and *N*-acetylcysteine) increases the risk of death and hospitalisation in patients with IPF [10], supporting a potential role for infection in disease progression.

In this chapter, we critically review the evidence for a role of infection in the pathogenesis and progression of ILDs, with emphasis on IPF, and the rationale for the use of antibiotics in these difficult-to-treat diseases.

Viruses and IPF

A number of studies have investigated the role of virus infections, as either the aetiological agent or as a contributor to disease progression in IPF, but the results have been inconsistent (table 1) [11].

Hepatitis C virus

Hepatitis C virus (HCV) has been investigated in lung fibrosis owing to its known ability to cause liver fibrosis. In a Japanese study, Ueda *et al.* [12] found HCV antibodies in 28% of IPF patients but only in 3.6% of controls. In addition, Arase *et al.* [13] observed 10- and 20-year cumulative incidences of IPF of 0.3% and 0.9%, respectively, in a cohort of 6150 patients with HCV compared with no cases of IPF in a control group of 2050 patients with hepatitis B virus. However, the association of HCV with IPF has not been observed consistently [14], although one study reported an association between HCV and a range of nonfibrotic lung diseases [15].

Human herpesviruses

Human herpesviruses (HHVs), a large family of ubiquitous DNA viruses that includes common pathogens such as HHV-1 (herpes simplex virus type 1), HHV-4 (Epstein–Barr

Table 1. Summary of the main associations of infectious agents with idiopathic pulmonary fibrosis (IPF)

Microorganism(s)	Putative role in IPF	Comment
Hepatitis C virus	Disease pathogenesis	Inconsistent results; unlikely to play a major role in IPF
Epstein–Barr virus	Disease pathogenesis	Increased frequency of the virus in lung biopsy and BAL samples from IPF patients
Herpesvirus saimiri	Disease pathogenesis	Viral DNA is found in lung epithelial cells of IPF biopsies
Torque teno (transfusion-transmitted) virus	Disease progression or trigger of acute exacerbation	Torque teno virus infection also present in patients with acute lung injury
***Prevotella*, *Veillonella* and *Escherichia* spp.**	Disease pathogenesis	Found in BAL samples from IPF patients but well-known colonisers of the healthy lung microbiome
***Streptococcus* OTU 1345 and *Staphylococcus* OTU 1348**	Disease progression	Found in BAL samples, as well as lung explants from IPF patients
***Haemophilus*, *Streptococcus*, *Neisseria* and *Veillonella* spp.**	Disease pathogenesis and progression	Higher levels in BAL samples from IPF patients compared with healthy controls and patients with COPD; at baseline, the BAL overall bacterial burden is higher in patients with IPF than in controls and predicts functional decline and risk of death

OTU: operational taxonomic unit.

virus (EBV)), HHV-5 (cytomegalovirus), HHV-7 and HHV-8 (Kaposi's sarcoma-associated herpesvirus), have received the greatest attention as either a causative or exacerbating factor in IPF [11]. This is mainly because of the ability of HHVs to establish life-long latency in the alveolar epithelium, with the potential to reactivate and cause disease in older individuals [16]. In the first study to suggest an association between HHVs and IPF, 12 out of 13 IPF patients were found to be seropositive for EBV compared with none of the 12 diseased controls with other forms of ILD [17]. An increased frequency of EBV in lung biopsy and BAL samples from IPF patients compared with controls has been reported by several other studies [18–21]. In addition, Tang *et al.* [22] found that 97% of patients with IPF had evidence of past infection with at least one HHV, compared with only 36% of controls. Recently, Folcik *et al.* [23] found herpesvirus saimiri (HVS) DNA in the regenerating epithelial cells of all 21 IPF biopsies tested but in none of the 21 control lung epithelial cells. HVS is a nonpathogenic virus of squirrel monkeys, its natural host, but has been shown to infect up to 7% of humans. While the transmission of HVS to patients with IPF remains unclear, the low frequency of this infection in humans is theoretically in keeping with HVS being an aetiological agent of an uncommon disease such as IPF. A seminal study by Lawson *et al.* [24] suggested a mechanistic link between viral infection and the development of IPF. Indeed, they observed that HHV-infected epithelial cells from patients with IPF (either sporadic or familiar) had evidence of endoplasmic reticulum stress and apoptosis, as shown by markers of the unfolded protein response. In turn, activation of

 https://doi.org/10.1183/2312508X.10005916

these pathways has been shown to promote the development of IPF [25]. In further support of a pathogenic role for viral infection in IPF, KROPSKI *et al.* [26] observed increased herpesvirus DNA in cell-free BAL along with evidence of herpesvirus antigen expression in alveolar epithelial cells in asymptomatic relatives of patients with familial IPF, suggesting that lung epithelium of individuals at risk for IPF may be infected with herpesviruses well before the disease becomes clinically evident.

While a growing body of evidence suggests a role for viruses in the pathogenesis of IPF, the studies performed to date have been retrospective in design and have been undertaken in relatively small patient populations. Furthermore, association does not imply causation, and a causal relationship between viruses and IPF has yet to be demonstrated.

The lung microbiome in IPF

Accumulating data, including an RCT showing that cotrimoxazole treatment is associated with reduced mortality in patients with IPF [27], suggest a potential role of the bacterial lung microbiome in the initiation and progression of IPF. However, our current understanding of the role played by bacteria in the pathogenesis of respiratory diseases, including IPF, derives largely from culture-based microbial studies. More recent high-throughput DNA sequencing technologies have enabled the rapid identification of complex bacterial communities (including organisms that cannot be cultured) based on sequence similarities in highly conserved genes, such as the gene for 16S ribosomal RNA (rRNA). These new tools, which have been extensively and successfully applied to, among others, gut, skin and oropharyngeal cavity microbial communities, are expanding our understanding of the abundance and diversity of microbial cells on and within the human body [28, 29].

RICHTER *et al.* [30] investigated bacterial colonisation of the lower airways in patients with granulomatosis with polyangiitis, healthy controls and patients with IPF, who served as diseased controls. Interestingly, they observed pathogen growth (*e.g. Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa* and *Proteus mirabilis*) in the BAL fluid of eight out of 22 (36%) IPF patients, suggesting that occult bacterial infection may be responsible for the alveolar epithelial injury observed in IPF. Subsequently, GARZONI *et al.* [31] examined BAL fluid and oropharyngeal swabs in 18 patients with ILDs (five with IIP, six with non-IIP and seven with sarcoidosis), six immunocompromised patients and nine healthy controls. However, ultradeep 16S rRNA gene sequencing did not reveal significant differences in the composition of lower airway microbiota, which consisted primarily of *Prevotellaceae*, *Streptococcaceae* and *Acidaminococcaceae*, across the five different patient subsets. HAN *et al.* [32] used culture-independent techniques based on 454 pyrosequencing of BAL samples (n=55) collected as part of the Correlating outcomes with biochemical markers to estimate time-progression in IPF (COMET) study, a prospective observational study. The most commonly identified bacteria were *Prevotella*, *Veillonella* and *Escherichia* spp. However, the study did not have negative sampling controls, and species of these three genera are well-known colonisers of the healthy respiratory microbiome. In addition, and perhaps more importantly, the presence of a specific *Streptococcus* sp. (operational taxonomic unit (OTU) 1345) or *Staphylococcus* sp. (OTU 1348) was strongly associated with disease progression, defined as a composite of death, acute exacerbation, lung transplant, or relative decline in forced vital capacity (FVC) $\geqslant$10% or diffusion capacity of

the lung for carbon monoxide (*D*LCO) ⩾15% over 48 weeks. Notably, *Streptococcus* OTU 1345 and *Staphylococcus* OTU 1348 were also identified in two independent lung explants from IPF patients (*i.e.* in the absence of bronchoscopy), suggesting that these bacteria were not contaminants coming from the upper airways. Interestingly, recent work has identified pneumolysin, a *Pneumococcus*-produced toxin, as a mediator of disease progression in mouse models of experimentally induced pulmonary fibrosis *via* injury of the alveolar epithelium [33]. Molyneaux *et al.* [34] explored the lung bacterial burden and composition in patients with IPF using 16S rRNA gene quantitative PCR and high-density pyrosequencing. They found a statistically significant 2-fold higher bacterial burden in the BAL of patients with IPF (n=65) compared with that of healthy controls (n=27) or patients with COPD (n=17). Furthermore, and perhaps more interestingly, bacterial burden at baseline predicted the rate of functional decline and risk of death. Notably, the increased risk of death associated with a high bacterial burden (hazard ratio 4.6) is comparable to that associated with a decline in lung function over 6 months, the current prognostic standard in IPF [35]. Subsequent pyrosequencing revealed increased reads of *Haemophilus*, *Streptococcus*, *Neisseria* and *Veillonella* spp. in IPF patients compared with controls, whereas there were no significant changes in bacterial community structure or composition between IPF patients with stable or progressive disease, although they differed in overall bacterial burden. Curiously, the association with higher bacterial burden was seen only in patients with IPF who did not carry the mutant allele of the *MUC5B* rs35705950 polymorphism, which has been associated with an increased risk of developing IPF but with improved survival among patients with established disease [36]. This observation raises the possibility that there may be two distinct pathways leading to alveolar injury in IPF: one involving higher bacterial load in individuals without the *MUC5B* variant and another in which MUC5B protein overexpression at the distal airway/alveolar junction results in increased local exposure or aberrant cellular responses to bacterial stimuli [37].

Role of infection in acute exacerbation of IPF

The term acute exacerbation of IPF (AE-IPF) refers to an acute (typically within <1 month), clinically significant respiratory worsening, characterised by new bilateral radiological abnormalities (ground-glass opacification/consolidation) not caused by cardiac failure, fluid overload or extraparenchymal causes, such as pulmonary embolism, pneumothorax or pleural effusion [38]. Such episodes, which are characterised histologically by diffuse alveolar damage, affect between 4% and 15% of IPF patients per year, and have a 3-month survival rate of ∼50% [38, 39]. Notably, AE-IPF shares many clinical, radiological and histopathological features with acute lung injury (ALI), which is known to be caused by, among others, infection, aspiration, drugs, massive transfusion and surgery [40], suggesting that, similar to ALI, AE-IPF may represent a response to external events (including infection), rather than an intrinsic acceleration of the underlying fibrotic disease.

Several studies have suggested a role for respiratory viral infection in AE-IPF, although respiratory viral RNA was detected in only a minority of patients [41–44]. A study of 43 subjects with AE-IPF failed to clearly identify a viral or other infectious aetiology for the acute event in the vast majority of patients [42]. In addition, all 43 subjects had negative bacterial cultures and negative viral serology. Similarly, by PCR analysis of BAL fluid, only four samples tested positive for common respiratory viruses (*e.g.* rhinovirus, parainfluenzavirus or coronavirus), while there was no evidence of detectable viruses on PCR of the BAL fluid from a group of IPF patients with stable disease (n=40). Conversely,

 https://doi.org/10.1183/2312508X.10005916

pan-viral microarrays revealed the presence of HSV (n=1), EBV (n=2) and torque teno (transfusion-transmitted) virus (TTV; n=12) in patients with acute exacerbation but not in the stable disease group [42]. TTV is a single-stranded DNA virus originally identified in a patient with post-transfusion hepatitis. TTV infection, however, was present in a similar percentage of ALI controls, suggesting that infection with this virus may simply represent the consequence (rather than the cause) of the severe underlying inflammatory process [42]. Deep sequencing of a subset of acute exacerbation cases confirmed the presence of TTV but did not identify any additional viruses [42]. However, in contrast to other respiratory conditions where exacerbations are truly acute events, the onset of AE-IPF is generally more insidious. Therefore, it is possible that the triggering virus is no longer detectable by the time the exacerbation becomes clinically evident [5].

Antibiotic treatment in acute exacerbation of IPF

There are no proven effective therapies for AE-IPF [38]. However, many patients are still treated empirically with systemic corticosteroids, broad-spectrum antibiotics and supportive care (*e.g.* palliation of symptoms and correction of hypoxaemia with supplemental oxygen). The use of antibiotics is based mainly on the fact that patients with AE-IPF commonly present with fever and flu-like symptoms and exhibit elevated neutrophil counts in BAL fluid [45]. However, prolonged antibiotic courses in patients with AE-IPF in whom no pathogens have been identified may increase the risk for subsequent fungal infections and a higher incidence of drug-resistant organisms [46].

Ding *et al.* [47] examined whether PCT-guided antibiotic treatment, compared with standard clinician-determined antibiotic treatment, reduced antibiotic prescription and the duration of therapy in patients with AE-IPF. 39 patients were assigned to the PCT-guided treatment group and 39 patients to the routine treatment group. Baseline characteristics, including demographics, clinical characteristics and laboratory results, were similar between the two groups. PCT guidance (*e.g.* PCT levels >0.25 $ng \cdot mL^{-1}$) significantly reduced the duration of antibiotic treatment (8.7±6.6 *versus* 14.2±5.2 days in the routine treatment group; p=0.0001). However, the duration of mechanical ventilation and mortality were similar in both groups.

Recently, Kuse *et al.* [48] retrospectively evaluated the long-term effect of macrolides, either alone or combined with conventional treatment (*e.g.* corticosteroids, or immunosuppressive or antifibrotic agents), on acute exacerbation and mortality in a cohort of Japanese patients with IPF (n=52). During the 36-month observation period, patients treated with macrolides had significantly less AE-IPF (13.8% *versus* 34.8%) and longer acute-exacerbation-free periods (p=0.027) and overall survival (p=0.047) compared with patients in the nonmacrolide group, suggesting a potential benefit of long-term macrolide therapy in patients with IPF.

Antibiotic treatment in other ILDs

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare, systemic neoplastic disease that almost exclusively affects women [49]. The disease may occur either sporadically or in the context of tuberous sclerosis complex, and is associated with cystic lung destruction, chylous fluid

effusions and abdominal tumours, including angiomyolipomas and lymphangioleiomyomas [49]. Sirolimus, also known as rapamycin, is a macrolide compound with immunosuppressive and anti-proliferative properties. By binding the intracellular protein FKBP12 (12 kDa FK506-binding protein), sirolimus forms an immunosuppressive complex that blocks the activation of the cell-cycle-specific kinase TOR (target of rapamycin) [50]. Following promising results from two uncontrolled studies [51, 52], the MILES (Multicenter international LAM efficacy of sirolimus) trial, a double-blind randomised parallel-group trial, enrolled 89 patients with LAM and moderate lung impairment (*e.g.* FVC <80%) who were randomly assigned to receive either sirolimus or placebo for 12 months followed by a 12-month observation period [53]. Sirolimus treatment resulted in stabilisation of lung function decline compared with placebo. In addition, while sirolimus-treated patients showed improvement in their FVC, placebo-treated patients experienced continuing worsening of their FVC (8±3 *versus* 11±3 mL per month, respectively; p=0.001). Moreover, quality of life measured by the EuroQol scale improved in the sirolimus group and declined in the placebo group (0.39±0.19 *versus* −0.21±0.20 units per month, respectively; p=0.03). However, in patients treated previously with sirolimus, the lung function decline resumed and paralleled that of the placebo group during the subsequent 12-month observation period in which sirolimus was withdrawn. One open-label uncontrolled trial and several case reports support the effectiveness of sirolimus in chylous effusions [54]. Accordingly, the American Thoracic Society/Japanese Respiratory Society guidelines on LAM recommend treatment with sirolimus for patients with abnormal/declining lung function (strong recommendation based on moderate-quality evidence) and with symptomatic chylous effusions (conditional recommendation based on very low-quality evidence) [54].

Cryptogenic organising pneumonia

Cryptogenic organising pneumonia (COP) is an uncommon form of IIP. The disease, which affects the distal airways and alveoli, is characterised radiologically by patchy air space consolidation, clinically by signs/symptoms that mimic those of CAP and histologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue [55]. While corticosteroids represent the treatment of choice, macrolide antibiotics, by virtue of their anti-inflammatory/immunomodulatory properties, may also have a role in the treatment of COP [56]. Stover and Mangino [57] reported on six patients (three with COP and three with organising pneumonia secondary to radiation therapy) who responded to clarithromycin, and suggested considering long-term macrolide therapy in patients with minimal symptoms and/or minimal physiological impairment, or as adjuvant therapy in patients receiving steroids or in those who cannot tolerate steroids. Recently, Ding *et al.* [58] performed a literature review and identified 35 cases of COP treated with macrolides (mostly clarithromycin, followed by erythromycin and azithromycin). Most patients improved, although the recovery was slower than that generally seen with corticosteroids. Overall, macrolide treatment was well tolerated. Based on these results, the authors recommended that macrolides might be used as a first-line treatment in patients with mild COP. However, which patients are likely to respond to macrolide therapy, and the appropriate dose and duration of treatment, are yet to be determined.

Clinical trials of antibiotics in IPF

A growing body of evidence supports the use of antibiotics in pulmonary fibrosis. Wuyts *et al.* [59] evaluated the effect of azithromycin (administered every other day from day 1

 https://doi.org/10.1183/2312508X.10005916

Table 2. Currently ongoing clinical trials evaluating the efficacy and safety of antibiotics in idiopathic pulmonary fibrosis (IPF)

Study name	Study design	Study duration	Estimated completion date	Primary outcome	Estimated enrolment n	Inclusion criteria	Trial identifier
Azithromycin for the treatment of cough in idiopathic pulmonary fibrosis – a clinical trial	Single-centre, prospective, double-blind, randomised, two treatments, two-period crossover; azithromycin 500 mg·day^{-1}, three times per week *versus* placebo	Two 12-week treatment periods separated by 4-week drug-free washout period	December 2018 (recruiting)	Subjective response to treatment (1.3 unit reduction of cough as measured with Leicester Cough Score)	25	Age ⩾18 years, IPF diagnosis, symptoms of cough	NCT02173145
Study of clinical efficacy of antimicrobial therapy strategy using pragmatic design in idiopathic pulmonary fibrosis (cleanUP-IPF)	Phase III, randomised, unblinded, multicentre; trimethoprim–sulfamethoxazole 160/800 mg twice daily or doxycycline 100 mg·day^{-1} if trimethoprim–sulfamethoxazole is not indicated	42 months	July 2019 (not yet recruiting)	Time to first nonelective respiratory hospitalisation or all-cause mortality	500	Age ⩾40 years, IPF diagnosis	NCT02759120
Pilot study phase III to evaluate the efficacy and safety trimethoprim–sulfamethoxazole in the treatment of idiopathic pulmonary fibrosis (TriSulfa-FPI)	Phase III, pilot-controlled; trimethoprim–sulfamethoxazole 80/400 mg (weight-adjusted) *versus* placebo	24 weeks	August 2016 (recruiting)	Decline in FVC ⩾5% at 24 weeks and/or hospitalisation for respiratory causes	56	Age 18–80 years, IPF diagnosis, ability to obtain a sample of sputum or oropharyngeal wash, FVC >50% predicted	NCT01777737
The efficacy and mechanism evaluation of treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole (EME-TIPAC)	Phase III, double-blind, parallel-group, randomised, placebo-controlled, multicentre; trimethoprim–sulfamethoxazole 160/800 mg twice daily *versus* placebo	Between 12 and 42 (median 27) months	June 2019 (recruiting)	Time to death (all causes), lung transplant or first nonelective hospital admission	330	Age >40 years, MRC dyspnoea score >1, on stable treatment regimen for at least 4 weeks[#], IPF diagnosis	EudraCT 2014-004058-32

FVC: forced vital capacity; MRC: Medical Research Council. [#]: oral prednisolone up to 10 mg·day^{-1}, antioxidant therapy, pirfenidone, nintedanib or other licensed medication for IPF.

onwards) compared with placebo on bleomycin-induced pulmonary fibrosis in mice. BAL and histology were performed at day 7 and day 35, and pulmonary function tests on day 35. At day 35, fibrotic changes were paralleled by a restrictive lung function defect, while BAL analysis revealed alterations in neutrophils and macrophages (innate immunity), as well as in T-helper (Th) 2, Th17 and T-regulatory cell cytokines (adaptive immunity). Interestingly, azithromycin reduced both the extent of lung fibrosis and the restrictive lung function pattern. The reason behind the beneficial effect of azithromycin on experimentally induced pulmonary fibrosis can only be speculated, but it may relate to its ability to modulate the innate and adaptive immune response.

Following a pilot study of 20 patients with progressive fibrotic lung disease in which cotrimoxazole treatment improved FVC, shuttle walk distance with reduced oxygen desaturation during exercise, Medical Research Council (MRC) dyspnoea score and St George's Respiratory Questionnaire symptom score [60], a larger randomised double-blind placebo-controlled parallel-group clinical trial was designed to assess the safety and efficacy of oral cotrimoxazole (960 mg twice daily) for 12 months, in addition to the usual treatment in patients with fibrotic IIP (definite or probable IPF n=170; definite or probable nonspecific interstitial pneumonia n=11) [27]. No significant differences between treatment groups were seen for change in FVC, the primary outcome. Likewise, no difference between the cotrimoxazole and placebo groups was observed in terms of change in *D*LCO, 6-min walk test or MRC dyspnoea score in the intention-to-treat analysis. Conversely, in the per-protocol analysis, cotrimoxazole treatment was associated with a significant improvement in EuroQol-5D-based utility (a measure of health state), a significant reduction in the percentage of patients requiring an increase in oxygen therapy and a significant reduction in all-cause mortality compared with placebo (cotrimoxazole: three out of 53; placebo: 14 out of 65; hazard ratio 0.21; p=0.02). This latter finding was probably due to a reduction of respiratory infection. In fact, patients receiving the "usual" immunosuppressive treatment were more likely to die if they were in the placebo group, whereas baseline immunosuppressive therapy did not have an effect on mortality in the cotrimoxazole group. However, the study had important drawbacks, including the lack of a true placebo arm and a high rate of dropout due to side-effects (mostly rash and nausea) among patients receiving cotrimoxazole (30% (28 out of 92) *versus* 8% (seven out of 86) in the placebo group).

A phase III double-blind parallel-group randomised placebo-controlled multicentre clinical trial of oral cotrimoxazole *versus* placebo in 330 patients with moderate and severe IPF is currently underway (Efficacy and mechanism evaluation of treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole (EME-TIPAC); EudraCT, trial number 2014-004058-32). The primary outcome will be the time to death (all causes), lung transplant or the first nonelective hospital admission, with results expected in 2019.

Table 2 summarises currently ongoing clinical trials evaluating the efficacy and safety of antibiotics in IPF.

Conclusions

Infectious agents have the potential to cause alveolar epithelial cell damage and the ability to modulate the host response to injury. Despite this, the role of the lung microbiome in the development, progression and exacerbation of ILDs, mostly IPF, has started to be

 https://doi.org/10.1183/2312508X.10005916

investigated only recently as a result of the availability of culture-independent molecular techniques that allow a detailed analysis of lung pathogens. The studies performed so far strongly support a potential role for infections as a cofactor in the development and progression of the fibrotic process or as a trigger of disease exacerbation in IPF. The application of these methodologies to larger populations of carefully characterised patients with IPF will hopefully clarify the role played by the lung microbiome in IPF, leading to the development of novel treatments for this fatal disease.

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Disclosures: P. Spagnolo has received personal fees from Roche/Genentech, InterMune, Santhera Pharmaceuticals, Boehringer Ingelheim and Novartis. He has also received nonfinancial support from Roche/Genentech and Boehringer Ingelheim.

Chapter 17

Insights into antibiotic use in children with CAP

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CAP remains a common illness and is a major cause of childhood morbidity worldwide. The use of treatment algorithms in industrialised countries has led to lower mortality rates. However, given the rate of development of antimicrobial resistance, the future of this approach is uncertain. Over the past decade there has been a dramatic increase in the prevalence of antimicrobial resistance in respiratory pathogens, which is related primarily to antimicrobial agents in common use. This observation, in both hospital and community settings, indicates that paediatricians must be made aware of the prevalence of antimicrobial resistance and have a basic understanding of its mechanisms, implementing antimicrobial stewardship programmes to ensure that the most appropriate antimicrobials are selected when initiating therapy. In this chapter, we discuss the aetiology of paediatric CAP as well as its severity, and the diagnostic methods used to identify the optimal first- and second-line antibiotic approaches for children with CAP. We conclude that improvements in diagnosis, treatment and prevention must be made to successfully reduce or prevent childhood CAP.

Cite as: Esposito S, Lelii M, Tenconi R, *et al.* Insights into antibiotic use in children with CAP. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 276–288 [https://doi.org/10.1183/2312508X.10019416].

Acute LRTIs are an important cause of global child mortality, accounting for approximately 1.4 million deaths annually of children <5 years of age [1, 2]. Among this group of pathologies, CAP has a special importance. CAP is generally defined as an infectious lung disease that was not acquired in a hospital. The presence of pneumonia can be verified by consolidating radiological findings. Without this confirmation, the term "acute LRTI" is preferred because it is impossible to differentiate clinical pneumonia from either bronchiolitis or acute bronchitis [3]. In developing countries, CAP is an important cause of death in children, whereas in developed countries, CAP is one of the major causes of morbidity among children ⩽5 years of age [4, 5]. CAP is therefore an important infectious disease due to its clinical, social and economic burden.

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It is generally agreed that well-timed and opportune therapy is essential to reduce the impact of this disease [3, 6, 7]. Nevertheless, there is no standard agreement for CAP diagnosis in Europe and there is also no clear consensus for prescribing antibiotics to paediatric CAP patients. Moreover, it is difficult to establish the aetiology of paediatric CAP because available biomarkers do not permit different aetiologies to be distinguished [7–10]. Furthermore, although MDR bacteria are in general rare in CAP [11], there is the increasing problem of antibiotic resistance and the immunisation coverage against respiratory pathogens varies widely throughout the world [7–10].

Aetiology of CAP in paediatric patients

Unfortunately, it is extremely difficult to identify the microorganisms that cause CAP in paediatric patients for various reasons. First, it is difficult to obtain secretions of the lower airways during the first years of life and invasive methods (*i.e.* bronchoscopy and BAL) are used when there is a clinical indication, as in the case of persistent or recurrent pneumonia or pneumonia in an immunocompromised patient [7, 9]. Second, cultures of the upper airways may be confounding because the normal flora of this site often includes bacteria that are commonly responsible for CAP [4]. Consequently, in clinical practice, we should consider the aetiology of paediatric CAP on the basis of the main pathogens identified in epidemiological studies involving children of different age groups [7, 12, 13].

A very large number of microorganisms can cause childhood pneumonia. Viruses appear to be responsible for 30–67% of CAP cases in childhood and they are more frequently observed in children <2 years of age [14, 15]. The most frequently observed viruses are respiratory syncytial virus and rhinoviruses, followed by influenza A and B viruses [15–17]. Other possible aetiological viruses include parainfluenza viruses, adenovirus, metapneumovirus, bocavirus and coronavirus [15, 18–22]. Viral and bacterial co-infections have been detected in ∼30–40% of patients, [5]. Although the existence of healthy carriers of viruses has been well documented, the presence of viral pathogens in the upper respiratory tract is usually considered to be evidence of a viral aetiology [23].

Bacteria are less frequent than viruses as aetiological agents of paediatric CAP, but the difficulties in distinguishing viral and bacterial CAP explain why in several cases antibiotics are recommended on the basis of the epidemiological distribution of bacteria in different age groups. Table 1 summarises the main bacteria associated with CAP in paediatric patients. The most frequent pathogens are *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*, although differences have been observed in different age groups. *S. pneumoniae* is the main bacterial pathogen of CAP in patients <5 years of age and is responsible for ∼30% of all cases [3, 6, 7]. The use of real-time PCR has increased our knowledge of *S. pneumoniae* CAP by revealing that DNA can still be detected in the blood in cases with negative blood cultures for this pathogen [24, 25]. In addition, PCR has clarified the contribution of different pneumococcal serotypes by showing that serotypes 1, 3 and 5 are primarily involved in complicated CAP, and serotype 19 is involved in invasive CAP [24, 25]. *S. pneumoniae* is commonly detected in cultures and by PCR of nasopharyngeal secretions from children even when they are healthy, reaching a prevalence of 80% in children <6 years of age [26]. This finding indicates that *S. pneumoniae* detection in the upper respiratory tract should be considered a possible cause of CAP only when alveolar CAP is present [27, 28].

Table 1. Main bacterial pathogens associated with CAP in paediatric patients

Species	Age group			
	Birth–1 month	1 month–3 months	3 months–5 years	5 years–18 years
Streptococcus pneumoniae	+	+++	++++	+++
Haemophilus influenzae [#]	±	+	+	±
Streptococcus pyogenes	–	+	+	+
Staphylococcus aureus	++	++	+	+
Streptococcus agalactiae	+++	+	–	–
Escherichia coli	++	+	–	–
Mycoplasma pneumoniae	–	+	+++	++++
Chlamydophila pneumoniae	–	+	+	++
Chlamydophila trachomatis	+	++	–	–
Bordetella pertussis	+	++	+	+

++++: very common; +++: common; ++: relatively uncommon; +: rare; ±: very rare; –: absent.
[#]: mainly untypeable because of the widespread use of the *H. influenzae* type b (Hib) vaccine.

M. pneumoniae has more recently emerged as an important cause of CAP in paediatric patients. Its prevalence is age dependent and, according to several authors, this pathogen represents the main aetiological agent of CAP in children ⩾5 years of age [29–32]. As with viruses, *M. pneumoniae* colonisation is usually regarded as an uncommon phenomenon and its presence in upper respiratory secretions is considered to be associated with an aetiological role for this pathogen [28]. However, a single-site study performed some years ago on a limited sample size showed that *M. pneumoniae* was equally present in asymptomatic and symptomatic children [33].

Regarding other types of bacteria, the main pathogens are *Streptococcus agalactiae*, *Escherichia coli* and *Chlamydophila trachomatis* during the first 3 months of life [7]. *S. agalactiae* and *E. coli* are transmitted during passage through the birth canal, and pneumonia is the manifestation of early sepsis. However, the pathogenic features of *C. trachomatis* are clinically manifested from 3 weeks of life until 6 weeks. Another pathogen that could be detected during the first 3 months of life is *Bordetella pertussis*. This bacterium continues to circulate despite immunisation programmes in various countries due to the limited persistence of the immunity and the suboptimal efficacy of the acellular pertussis vaccine [34].

Regarding *Haemophilus influenzae*, the importance of type b (Hib) has been declining since the inclusion of Hib in the hexavalent and pentavalent formulations of vaccines that are universally recommended during the first years of life in the majority of countries [7]. Data regarding the existence of untypeable strains of *H. influenzae* in paediatric patients are lacking due to the difficulties in diagnosis [28].

Other bacterial pathogens, such as *Staphylococcus aureus*, *Streptococcus pyogenes* and *Chlamydophila pneumoniae*, appear to be less frequent causes of CAP. *S. aureus* is detected in some severe and complicated cases, and may be observed in premature neonates and immunosuppressed patients [7]. *S. pyogenes* is sometimes detected in children >3 months of age, whereas *C. pneumoniae* is reported mainly in children >5 years of age, but it seems primarily to be a co-pathogen [7, 29, 30].

 https://doi.org/10.1183/2312508X.10019416

Several studies over the past 20 years have shown that the various different pathogens have several similarities in terms of clinical presentation, laboratory biomarkers and chest radiography [28, 29, 35, 36]. Consequently, the conclusion for clinical practice is that it is not possible to identify the correct aetiology of CAP in a single patient using clinical, laboratory and radiographic data, and the empirical antibiotic treatment for paediatric CAP should be based on diagnostic algorithms that begin with the age of the patient given the age-related importance of different pathogens.

Antibiotic resistance in children with CAP

Although antibiotic resistance in CAP is rare [11], it should be considered in the establishment of proper therapeutic indications [37].

Overall, the resistance of *S. pneumoniae* to penicillin and other β-lactams is related to target-mediated changes in the size and configuration of the penicillin-binding proteins (PBPs) that enable the cross-linking of bacterial cell wall precursors [37]. There are different degrees of resistance, ranging from low-level to high-level resistance [38]. The susceptibility of *S. pneumoniae* to penicillin and β-lactams shows wide variations across European countries. As described in the Annual Report of European Antimicrobial Resistance Surveillance Network (EARS-Net) regarding the period 2011–2014, the percentage of penicillin-nonsusceptible isolates ranged from 0% (Cyprus) to 46.7% (Romania) [38]. Significantly increasing trends were observed in Italy and Sweden. Resistance rates of 25–50% were reported in Bulgaria, Romania, Croatia and Spain; rates of 10–25% were reported in France, Finland, Hungary, Ireland, Slovakia, Lithuania, Finland, Italy and Portugal; rates of 5–10% were reported in Luxembourg, the Czech Republic, Estonia, Sweden, Slovenia, Denmark, Latvia, Norway and the UK; and rates of 1–5% were reported in Austria, Belgium, Germany, Estonia, Iceland and the Netherlands [38]. Low-level resistance and intermediate-level resistance were the types of resistance most frequently detected in all of the countries. Interestingly, clinical studies have shown that *S. pneumoniae* strains with reduced susceptibility to penicillin can usually be eradicated by standard treatment, regardless of the β-lactam antibiotic, when the distribution of the drug at the site of infection makes it possible to reach tissue concentrations that are similar to or even higher than those usually present in the blood [37]. As this is the case in the lung, it is easy to understand why several papers have demonstrated that the outcomes of pneumococcal pneumonia caused by strains currently defined as having reduced susceptibility to penicillin are often good, regardless of the drug used [39–41].

The resistance of *S. pneumoniae* to macrolides has increased consistently since first being described in 1952 [37]. It is linked to three different mechanisms: alterations in the ribosomal target site, production of inactivating enzymes, and production and use of the active efflux pump. The first of these mechanisms is the most frequent and determines high-level resistance with broad cross-resistance to macrolides, lincosamides and streptogramin B [37]. Macrolide nonsusceptibility is higher in most countries than penicillin nonsusceptibility. The rates varied from <1% (Cyprus) to 48.0% (Romania) in 2011–2014 according to EARS-Net [38]. Resistance rates of 25–50% were observed in Malta, Italy, Croatia, Slovakia, Bulgaria and Romania; rates of 10–25% were observed in Portugal, Spain, France, Luxemburg, Belgium, Ireland, Finland, Lithuania, Austria, Hungary and Slovenia; rates of 5–10% were observed in the Czech Republic, Germany, the UK, Denmark, Norway, Sweden, Iceland and Estonia; and rates of 1–5% were observed in Latvia and the

Netherlands [38]. Over the past few years, there have been an increasing number of reports of macrolide treatment failure in cases of pneumococcal CAP in clinical practice [37, 42–44]. Based on this observation and the difficulties in routinely evaluating the characteristics of resistance in pneumococcal strains, it can be concluded that macrolides cannot be used as single agents to treat pneumococcal CAP in the presence of *in vitro* resistance or in those areas where the global resistance of *S. pneumoniae* is particularly high.

Regarding *M. pneumoniae*, macrolides are the first line of treatment for this pathogen, although some authors have raised doubts about the need to treat it [45]. According to the Cochrane review published by Gardiner *et al.* [45], there is insufficient evidence to draw any specific conclusions about the efficacy of antibiotics for CAP associated with *M. pneumoniae* infection in children (although one trial suggests macrolides may be efficacious in some children with LRTI secondary to *Mycoplasma*). The authors of the Cochrane review concluded that the use of antibiotics has to be balanced with possible adverse events and that there is still a need for high-quality double-blinded RCTs to assess the efficacy and safety of antibiotics for LRTI secondary to *M. pneumoniae* in children. Moreover, outbreaks of CAP due to *M. pneumoniae* that are resistant to macrolides have been reported recently [44, 46]. The prevalence of *M. pneumoniae* macrolide resistance ranges from 0–15% in Europe and the USA to up to 90% in some outbreaks in Asia [44, 46]. *M. pneumoniae* macrolide resistance should be considered in patients with *M. pneumoniae* infection that persists with fever after 4 days of antimicrobial therapy, including macrolides [47, 48]. However, a number of cases that were treated with ineffective antibiotics have shown similar outcomes in children with CAP due to *M. pneumoniae* strains that were resistant to macrolides and those with susceptible strains [44]. This result seems to indicate that there is no need to systematically change macrolide use in cases of mild to moderate disease, but other antibiotics should be prescribed if the symptoms persist or if there are signs of clinical deterioration. In cases of documented CAP caused by *M. pneumoniae* resistant to macrolides, levofloxacin has been associated with a positive clinical evolution [44, 48].

Regarding the less common pathogens involved in CAP, it is important to mention the emergence of MRSA. The mechanism of resistance of *S. aureus* to methicillin and all other β-lactam agents is due to a variant of PBP2a that prevents the inhibition of cell wall synthesis by β-lactams [49]. In addition, community-acquired MRSA strains that were Panton–Valentine leukocidin-positive have been reported [50]. As reported by EARS-Net, the rate of MRSA in Europe ranges from 0.9% to 56.0% [38]. The rates of MRSA were generally lower in Northern Europe and higher in the Southern Europe. CAP due to MRSA appears to be characterised by a severe clinical presentation that is frequently associated with complications [6, 7]. These cases require the use of active drugs such as glycopeptides and linezolid [6, 7].

Moreover, most of the *H. influenzae* strains that are not susceptible to aminopenicillins produce TEM-1 and ROB-1 β-lactamases, both of which are sensitive to inhibitors such as clavulanic acid [37]. This resistance can therefore be overcome by prescribing an aminopenicillin together with an inhibitor or a different β-lactam antibiotic that is resistant to β-lactamases. Although the older macrolides have limited activity against *H. influenzae*, their newer counterparts (especially azithromycin) are effective against most strains [51]. In β-lactamase-negative ampicillin-resistant *H. influenzae* strains, the most frequent mutation is localised to the *ftsI* genes encoding PBP3A and/or PBP3B, which are involved in septal peptidoglycan synthesis [37]. The prevalence and impact of these strains on children with CAP is currently unknown.

 https://doi.org/10.1183/2312508X.10019416

Finally, the problem with *S. pyogenes* is that it is often resistant to macrolides. The rate varies, but reaches 30% in countries such as Italy, Greece, the Slovak Republic and Spain, as well as in Asian countries [52]. However, the risk of failure with macrolides that was highlighted for *S. pneumoniae* also needs to be taken into account and β-lactams should be considered as first-line agents.

Thus, there has been a dramatic increase in the prevalence of antimicrobial resistance in respiratory pathogens over the past two decades, much of which is related to commonly used antimicrobial agents. These findings, in both hospital and community settings, indicate that paediatricians must be made aware of the prevalence of antimicrobial resistance and have a basic understanding of its mechanism to ensure that the most appropriate antimicrobials are selected when initiating therapy. In this regard, the implementation of antimicrobial stewardship strategies appears extremely important to preserve the activity of existing antimicrobial agents [53].

Severity assessment of CAP

Although chest radiography is the gold standard for CAP diagnosis, it is not necessary for the confirmation of suspected CAP in previously healthy children with mild to moderate respiratory symptoms who do not require hospitalisation [6, 7, 9]. However, chest radiography is essential in the management of severe and/or recurrent CAP to confirm the diagnosis, evaluate the extension of the parenchymal infiltrate and exclude the presence of complications requiring a target therapy. Complications include empyema, necrotising pneumonia, pneumatoceles and lung abscesses, and in the presence of these conditions long-term intravenous antibiotic administration, in some cases with anaerobic coverage, as well as pleural fluid drainage or other surgical procedures could be required [54].

Assessment of the severity of CAP is essential for determining the necessity of further clinical examinations and the appropriate treatment setting. Mild to moderate CAP can be managed safely in an outpatient setting, whereas severe CAP can be life threatening and requires hospital-based care [54]. Unfortunately, although scoring systems for severity have been developed and validated for adults with acute LRTI, such tools do not exist to predict the clinical severity requiring hospitalisation for children. In the paediatric age group, the severity of pneumonia is assessed by the child's overall clinical appearance and behaviour, including an assessment of his/her degree of alertness and willingness to eat or drink. Any child who presents "danger signs" (including hyperpyrexia $\geqslant$39°C and tachycardia, a capillary refill time of >2 s, dehydration, and respiratory distress) should be hospitalised [3, 6, 7]. The major criterion for inpatient treatment of CAP is hypoxaemia, which can be associated with age-adjusted tachypnoea, retractions, grunting and nasal flaring, and can increase the risk of death [3, 6, 7]. Age-adjusted tachypnoea is a marker of respiratory distress, although it is not specific because it can be caused by fever, dehydration or concurrent metabolic acidosis [7]. Experts agree that blood oxygenation is an essential factor for evaluating CAP severity and the best indicator of the need for hospitalisation [3, 6, 7]. European guidelines consider arterial oxygen saturation ($P\mathrm{aO}_2$) <92% as indicative of severe CAP [3, 7], whereas the US guideline indicates $P\mathrm{aO}_2$ <90% as the cut-off [6]. Additional indications include neonatal age, pre-existing comorbidities, suspected infection due to MRSA, difficulties in oral feeding, vomiting or inability of the parents/caregivers to manage the illness in the community [3, 6, 7].

Investigations of potential target therapies

As the signs and symptoms of viral and bacterial CAP may be very similar, and radiological findings are not helpful in distinguishing different aetiological agents, several attempts have been made to clearly identify the aetiology. Overall, there is no need to perform laboratory tests in mild to moderate cases of CAP, but investigations are required in severe cases.

Concerning nonmicrobiological laboratory tests, total and differential white blood cell counts and acute-phase reactants, including the erythrocyte sedimentation rate and CRP levels, are not helpful for decision making in individual cases [7, 54]. Several other serum biomarkers have been studied, but an increasing amount of evidence indicates that PCT is the best diagnostic marker for distinguishing bacterial CAP from viral CAP and reducing the duration of antimicrobial therapy [29, 37, 53–57].

Blood cultures have a low sensitivity and the proportion of positive blood cultures is often <10% [58, 59]. Therefore, a targeted approach that involves obtaining blood cultures only from those patients hospitalised with CAP who are identified to be at risk for bacteraemia seems to be more clinically effective and cost saving compared with a universal approach [60].

Molecular diagnostic assays of blood and pleural fluid can significantly improve the results obtained from blood cultures, primarily for *S. pneumoniae* [25, 26]. In addition, these assays facilitate the identification of viruses and atypical bacteria in nasopharyngeal secretions, which assists in the identification of CAP aetiology [61]. As noted earlier when discussing the aetiology of CAP in paediatric patients, the presence of *S. pneumoniae* DNA in nasopharyngeal secretions is not associated with a causative role of CAP because, apart from cases in which it is detected at high bacterial loads [28, 62], it mainly represents a carrier state.

Unlike in adults, sputum in children is often not adequate for contamination with upper respiratory secretions [7]. Similarly, urine collection for pneumococcal antigenuria is not indicated for paediatric patients as false-positive results frequently occur due to the high prevalence of nasopharyngeal pneumococcal colonisation [6, 7].

Regarding serology, its accuracy varies widely, and the need for both acute and convalescent samples limits its utility in epidemiological studies [12].

Overall, antibiotic therapy is usually prescribed on the basis of an algorithm that, in addition to the patient's age, also considers the severity of CAP.

Antibiotic management of CAP

Indications for treatment

Despite various efforts, the aetiology of CAP in children is not identifiable in most cases. For this reason, paediatricians are encouraged to prescribe empirical antimicrobial treatments to all children with a strongly suspected or confirmed diagnosis of CAP if the clinical signs and symptoms are severe [3, 6, 7]. Children with mild CAP who can be

 https://doi.org/10.1183/2312508X.10019416

closely followed up, and for whom all of the available epidemiological, clinical, laboratory and radiological data clearly suggest a viral infection, should be given symptomatic therapy alone [7]. However, a close follow-up should be assured and re-evaluation considered depending on the evolution of the disease.

Empirical treatment of CAP is based on the reported prevalence of different pathogens at different ages, antimicrobial resistance rates, clinical severity and the vaccination status of the child. Considering the importance of age in predicting the CAP-causative microorganisms, it is useful to consider an empirical treatment schedule based on the four different age groups in table 1: birth–1 month (neonates), 1 month–3 months (infants), 3 months–5 years (infants and pre-school-aged children) and 5 years–18 years (school-aged children and adolescents) [7, 9].

In neonates, a combination of ampicillin (or amoxicillin) and aminoglycosides (mainly gentamicin) is the first line of treatment, and ampicillin is strongly recommended if *Listeria monocytogenes* is suspected. However, although *L. monocytogenes* is not a common cause of pneumonia, its coverage is recommended in the regimen by several experts because pneumonia in a neonate could be the consequence of sepsis and could be associated with a potential risk of meningitis. Broad-spectrum parenteral cephalosporin can be used as an alternative treatment [7], although the use of third-generation cephalosporins in infants with extremely low birthweights may increase the risk of invasive candidiasis and the selection of ESBL-producing organisms [63]. Cefotaxime is preferred to ceftriaxone, especially in hyperbilirubinaemic or pre-term newborns, because of the high avidity of ceftriaxone to the serum proteins, including albumin, which transport bilirubin [64]. Staphylococcal pneumonia is rare. However, if blood or pleural fluid cultures grow *S. aureus*, oxacillin or vancomycin should be used in areas where MRSA is a reasonable possibility [7, 64]. Whenever *C. trachomatis* is suspected, clarithromycin or azithromycin are the recommended antibiotic options [65]. The use of erythromycin is discouraged in infants <6 weeks of age because of the risk of hypertrophic pyloric stenosis [66].

In infants 1–3 months of age, the treatment of choice is a β-lactam antibiotic acting against *S. pneumoniae*, which is the main bacterial cause of CAP at this age [7]. Macrolides are recommended if *C. trachomatis* or *Bordetella pertussis* is suspected, especially in cases with atypical presentations (*i.e.* apnoea, no fever and severe cough) [7].

Between the ages of 3 months and 5 years, several CAP cases have viral origins, so a "watchful waiting" approach could be recommended for previously healthy, appropriately immunised infants with mild to moderate pneumonia [7]. As the main causative agent of CAP is *S. pneumoniae*, oral amoxicillin or eventually ampicillin should be used as first-line therapy if a bacterial infection is suspected [7]. It is important to note that recent studies have demonstrated that oral amoxicillin given at a high dosage (*i.e.* 80–90 $mg \cdot kg^{-1} \cdot day^{-1}$) is as effective as injectable penicillin in the management of pneumonia of varying severity in high-resource settings [67]. Severe cases, clinical failures and children who are not fully immunised against Hib should be treated with amoxicillin–clavulanate or third-generation cephalosporins [7]. Starting from 2 years of age, *M. pneumoniae* may play a significant role, and macrolides are recommended by several authors in combination with a β-lactam in the absence of a clinical response with β-lactams only and in severe cases [9]. Experimental data show that macrolides are efficacious for their antimicrobial effect in addition to their immunomodulatory properties [33].

As *M. pneumoniae* is the most frequent pathogen in school-aged children and adolescents, macrolides are first-line drugs for mild to moderate CAP [7]. Although this recommendation is followed by several European and US experts [3, 7], the UK guideline does not include this recommendation and there is no indication for systematic treatment of *M. pneumoniae* infection [6]. In more severe cases, *S. pneumoniae* infection should be suspected and β-lactam therapy should be added to the treatment [7]. Quinolones should only be used in cases of bacterial resistance that cannot be overcome or in cases of IgE-mediated allergies to β-lactams, as they are not approved for the regular treatment of children and can lead to the selection of resistant strains or to adverse events, such as *Clostridium difficile* colitis or tendon disorders [7].

Finally, neuraminidase inhibitors should be prescribed to paediatric patients with influenza pneumonia during the influenza season [68].

Duration of treatment

The recommended duration of antibiotic treatment ranges from 7 to 14 days depending on the severity of CAP, but this was decided arbitrarily due to the lack of comparative studies [6, 7]. Some studies that were conducted in resource-poor settings have shown that significantly shorter courses of 3–5 days may be sufficient to cure children with CAP [69–71]. However, this evidence is weakened by the fact that the clinical criteria used may not have appropriately identified children with true bacterial pneumonia necessitating antibiotic treatment. A recent randomised trial in Israel found that oral treatment with amoxicillin for 5 days was as effective as a 10-day course in children 6–59 months of age with nonsevere alveolar CAP [72].

Regarding CAP complications (*i.e.* parapneumonic effusion, necrotising pneumonia, pneumatoceles and lung abscesses), comparative studies have not identified the optimal duration of therapy, but prolonging antibiotic treatment up to 3–6 weeks depending on the type of complication and on the clinical evolution is recommended [54].

Parenteral to oral switch therapy

RCTs involving children have not been conducted, but it is feasible to make a parenteral to oral switch of antimicrobial therapy in patients who present clear evidence of improvement, have remained afebrile for at least 24–48 h and are not experiencing diarrhoea or vomiting [7].

Conclusions

CAP remains a common illness and a major cause of childhood morbidity worldwide, possibly due to its complex aetiology. CAP characteristics in children are different from those reported in adults and unfortunately there are very few paediatric guidelines on paediatric CAP management [3, 6, 7]. Consequently, it is not possible to compare practices in children living in countries with high resistance rates and low resistance rates. The use of treatment algorithms in industrialised countries has led to lower mortality rates. However, given the rate of development of antimicrobial resistance, the future of this approach is uncertain. The prevalence of antimicrobial resistance in respiratory pathogens, such as *S. pneumoniae* and *H. influenzae*, has dramatically increased over the past decade, with

 https://doi.org/10.1183/2312508X.10019416

much of the increase being related to commonly used antimicrobial agents. This finding, in both hospital and community settings, indicates that paediatricians must be made aware of the prevalence of antimicrobial resistance and have a basic understanding of its mechanism, implementing antimicrobial stewardship programmes to ensure that the most appropriate antimicrobial choices are made when initiating therapy. The wider use of new pneumococcal conjugate vaccines over the next few years may represent an important advance in the reduction of pneumococcal CAP, but the long-term effects of immunisation are not clear.

To successfully reduce or prevent childhood CAP, improvements must be made in the diagnosis of the disease and the causes of individual cases must be elucidated. There is also a need for the development and maintenance of laboratory-based surveillance systems to provide clinicians and researchers with timely feedback regarding resistance rates. Our understanding of the role of individual antibiotics in the development of resistance also needs to be improved, as does the use of existing vaccines. Novel antimicrobial agents must also be developed. Finally, consensus guidelines for patient management and antimicrobial treatment, including antimicrobial stewardship programmes, should be refined over time and used by practitioners in their offices and in hospitals.

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Disclosures: S. Esposito has received grants from GSK, Roche, Novartis, Pfizer, DMG and Vifor. She has also received personal fees from GSK, Valeas and Vifor.

 https://doi.org/10.1183/2312508X.10019416

Chapter 18

New antibiotic development for pulmonary infections: New Drugs for Bad Bugs and beyond

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Antimicrobial resistance has been recognised as a public health threat on a global scale, causing at least 700 000 death cases every year, which is predicted to increase to 10 million deaths per year in 2050 if no measures to contain antimicrobial resistance are taken. This rapidly spreading menace has made many antibiotics obsolete, which, together with the slow pace of clinical development of new antibacterials, has nearly desiccated the antibiotic pipeline, leaving fewer treatment options for many infections, including LRTIs. The few recently approved antibiotics and molecules in the final stages of clinical development could potentially be the light at the end of the tunnel for the treatment of LRTIs. Concerted action is needed to effectively confront antimicrobial resistance and deliver novel strategies for the treatment of infections caused by MDR bacteria. A multidisciplinary network, such as that created under the New Drugs for Bad Bugs programme, would play a crucial role in improving the efficiency of anti-infective trials.

Cite as: Kostyanev T, Bonten MJM, Goossens H. New antibiotic development for pulmonary infections: New Drugs for Bad Bugs and beyond. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 289–301 [https://doi.org/10.1183/2312508X.10006116].

Since the discovery of the first antibiotic molecules and their use in clinical practice for the treatment of infections in the 1940s, antibiotic resistance has evolved and has been growing to reach its current endemic proportions. Antimicrobial resistance is currently recognised as a public health threat on a global scale, causing, according to some, at least 700 000 deaths every year, which is predicted to increase to 10 million deaths per year in 2050 if no measures to contain antimicrobial resistance are taken [1]. A Review on Antimicrobial Resistance publication suggested 10 crucial recommendations in their final report to tackle antimicrobial resistance, including an emphasis on the importance of increased awareness, infection prevention, better use of existing treatments, and reducing

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antibiotic use in agriculture and pollution of the environment [2]. Better and more effective antimicrobial stewardship measures are needed to preserve the few effective molecules in the pipeline that target MDR pathogens, as well as a robust approach to speeding up the development of novel antibacterials and feeding the antibiotic pipeline with new tools to combat antimicrobial resistance.

The rapidly booming rate of antimicrobial resistance in the past 20 years worldwide, which has made many antibiotics obsolete, and the slow pace of clinical development of new antibacterials have almost desiccated the antibiotic pipeline, leaving fewer treatment options for many infections (table 1), including LRTIs. Key antibiotics used in the treatment of LRTIs, such as carbapenems, fluoroquinolones and colistin [3–6], have been compromised by MDR and XDR pathogens. Resistance rates to these and other antibiotics have been increasing alarmingly in many countries, such as Greece, where carbapenem-resistant *Klebsiella pneumoniae* isolates accounted for 62.3% of all invasive *K. pneumoniae* isolates in 2014 [7]. Nonsusceptibility to fluoroquinolones also appears to be extremely high in both invasive *K. pneumoniae* (>60% in Greece, Poland, Romania and Slovakia) and *Pseudomonas aeruginosa* isolates [7]. The re-emergence of colistin as a therapeutic option and drug of choice in MDR infections and its broad use in the veterinary sector have led to

Table 1. Recently approved antibiotics for LRTIs

Antibiotic	Approved indications	Main adverse events (>1%)
Tigecycline	cSSTIs, cIAIs and CAP, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and "atypical organisms" (*Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*)	Nausea, vomiting, diarrhoea
Ceftaroline	cSSTIs and CAP, caused by MRSA or penicillin-nonsusceptible *S. pneumoniae*	Diarrhoea, nausea, rash, constipation, vomiting, increased transaminases, hypokalaemia, phlebitis, pyrexia, pruritus
Ceftazidime–avibactam	cIAIs and cUTIs, caused by cephalosporin-resistant Gram-negative pathogens	In cIAIs plus metronidazole: diarrhoea, nausea, vomiting, headache, dizziness, abdominal pain; in cUTIs: constipation, anxiety, abdominal pain, upper abdominal pain, dizziness
Tedizolid	SSTIs, caused by Gram-positive pathogens	Nausea, headache, diarrhoea, haemoglobin <10.1 $g \cdot dL^{-1}$, vomiting, platelets <112×10^3 cells$\cdot mm^{-3}$, dizziness
Telavancin	SSTIs and HAP/VAP, caused by MRSA or other Gram-positive organisms	Taste disturbance, nausea, vomiting, foamy urine, diarrhoea, dizziness, rigours, pruritus, rash

(c)SSTI: (complicated) skin and soft tissue infection; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection.

 https://doi.org/10.1183/2312508X.10006116

a rise in colistin resistance rates [6]. Furthermore, it has been found that, as well as the chromosomally encoded resistance, there is also a plasmid-mediated polymyxin resistance mechanism, MCR-1, in *Enterobacteriaceae* [8], which is highly transferable and may have the potential to become the next menace in the field of antimicrobial resistance [9].

New, recently approved antibiotics for LRTIs

Tigecycline

Tigecycline is a glycylcycline antibiotic approved in the USA in 2005 and licensed in 2006 in Europe for the treatment of patients with complicated skin and soft tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs) [10, 11]. Several studies have also shown its efficacy in patients with CAP and VAP [12–15]. Active against a number of pathogens causing CAP, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *K. pneumoniae* and "atypical organisms" (namely *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*) (figure 1), intravenous (*i.v.*) tigecycline was noninferior to *i.v.* levofloxacin and was well tolerated by hospitalised adults with CAP [13]. In comparative RCTs in hospitalised patients, a treatment regimen of tigecycline 100 mg *i.v.* once and then 50 mg *i.v.* twice daily had efficacy and safety comparable to the comparator agent [12]. Tigecycline is also well tolerated at a higher-than-standard dose in critically ill patients with severe infections [14], and in VAP patients, the high-dose regimen was associated with better outcomes than the conventional regimen [14]. The activity of tigecycline against *Acinetobacter baumannii* and other MDR/XDR Gram-negative organisms (except *P. aeruginosa*) makes it an appropriate drug of choice for the treatment of LRTIs caused by MDR pathogens. There is also evidence that the outcomes of treatment with tigecycline are comparable to those of colistin-based therapy for patients with MDR/XDR *A. baumannii* pneumonia [15].

Ceftaroline fosamil

Ceftaroline fosamil is approved for the treatment of cSSTIs and CAP in adults and children, and was marketed in 2012. Ceftaroline is a β-lactam active against MRSA and penicillin-nonsusceptible *S. pneumoniae* due to its affinity for the altered penicillin-binding

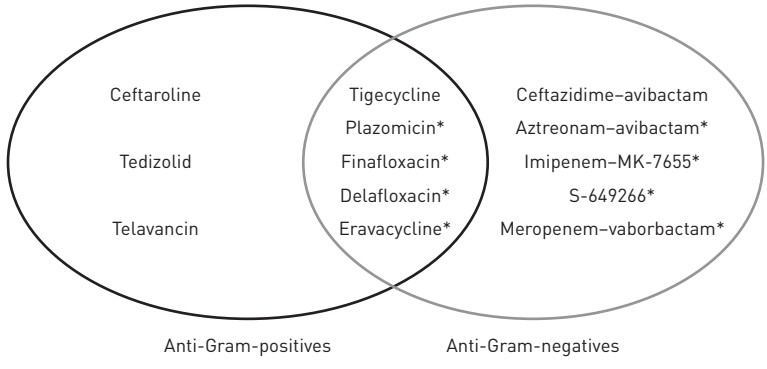

Figure 1. Spectrum of activity of recently approved antibiotics for LRTIs and of investigational drugs in later stages of clinical development (indicated with an asterisk).

proteins in these microorganisms. In a phase III RCT in Asia, ceftaroline fosamil 600 mg given every 12 h was superior to ceftriaxone 2 g given every 24 h for the treatment CAP [16]. Another extensive *in vitro* study on respiratory pathogens comprising isolates from 39 countries demonstrated that ceftaroline had superior *in vitro* activity compared with ceftriaxone [17]. However, the low coverage of Gram-negative pathogens and ineffectiveness against some MDR microorganisms, such as producers of ESBLs or carbapenem-resistant Gram-negative organisms, makes ceftaroline less attractive in LRTIs caused by such pathogens [18].

Ceftazidime–avibactam

Ceftazidime–avibactam has recently been added to the pool of available antibiotics after market authorisation for Europe was obtained in June 2016, and includes the indication for treatment of cIAIs, complicated urinary tract infections (cUTIs) and HAP, including VAP [19]. Ceftazidime is a third-generation antipseudomonal cephalosporin, while the broad-spectrum β-lactamase inhibitor avibactam protects ceftazidime from several classes of β-lactamases. The few clinical trials performed so far have reported that ceftazidime–avibactam is as effective as a carbapenem in cUTIs and cIAIs [20]. In several phase III studies, ceftazidime–avibactam was compared with the best available therapy and the proportions of patients with clinical cure at the test-of-cure visit were similar in both groups [21–23]. In another phase III trial, ceftazidime–avibactam was noninferior to meropenem in the treatment of adults with HAP/VAP [24].

Macrolides

Macrolides are part of all international guidelines for the treatment of CAP and acute exacerbation of COPD as an alternative to β-lactams for outpatients, and are frequently used in combination with β-lactams for severely ill patients in hospital [25]. Inappropriate use in the outpatient setting for viral LRTIs has stimulated resistance against these agents. Solithromycin is a novel macrolide from the group of ketolides, presenting with less toxicity than the first ketolide, telithromycin. There is some evidence that solithromycin has a better anti-inflammatory profile compared with "older" macrolides, making it a promising agent for the treatment of COPD [26]. In a phase III trial, solithromycin was noninferior to oral moxifloxacin in the treatment of CAP, confirming a previous study demonstrating noninferiority to levofloxacin in patients with CAP [27, 28].

Similar to the administration of other antibiotics for lung infections, such as tobramycin, colistin and aztreonam, inhalation of macrolides might be a new approach in the treatment of LRTIs [29]. There have been a limited number of *in vitro* and *in vivo* studies, and there is a need for more evidence on the efficacy of this route of administration.

Oxazolidinones

Tedizolid (formerly TR700) is one of the newer oxazolidinones approved for the treatment of acute bacterial SSTIs in the USA since 2014 and in Europe since 2015. Tedizolid is still investigational for the treatment of MRSA LRTIs [30], but is already considered as an alternative to linezolid because of its lower risk of myelotoxicity, higher penetration in the epithelial lining fluid, lower risk of drug–drug interactions with selective serotonin reuptake inhibitors and other advantages [31]. Several pharmaceutical companies are exploring the

 https://doi.org/10.1183/2312508X.10006116

opportunities to push this drug forward for the treatment of LRTIs. Many phase III clinical trials are ongoing, one of which is comparing a pro-drug of tedizolid, TR-701 FA, with linezolid for the treatment of ventilated subjects with suspected Gram-positive HAP/VAP (ClinicalTrials.gov, trial number NCT02019420). The indications for tedizolid, registered for SSTIs, may eventually be extended with the data collected from an ongoing phase IV clinical trial (ClinicalTrials.gov, trial number NCT02444234) in patients with cystic fibrosis. In murine models, tedizolid penetrated equally well in the epithelial lining fluid as linezolid [32], had comparable efficacy for MRSA pneumonia, and was even more effective against penicillin-susceptible and penicillin-resistant *S. pneumoniae* pneumonia than linezolid [33, 34].

Telavancin

Telavancin reached the European market in 2011 with a primary indication to cure nosocomial pneumonia, as well as HAP/VAP, caused by MRSA. It is a new lipoglycopeptide, with a broad coverage of Gram-positive pathogens, including MRSA and *S. pneumoniae* [35, 36]. This compound inhibits bacterial wall synthesis and disrupts the bacterial membrane to exert its bactericidal activity. Telavancin was noninferior to vancomycin for the treatment of HAP in two phase III studies, although a higher risk of nephrotoxicity and serious adverse events was observed compared with the vancomycin group [37, 38].

Efforts to stimulate antibiotic development for LRTIs

No new classes of antibiotics have been discovered within the past 20 years and there is an urgent need to refuel the antibiotic pipeline. Much effort has been made from both academia and industry to overcome antimicrobial resistance and fill the gap in the armamentarium of antibiotics [39, 40]. The Innovative Medicines Initiative (IMI) programme is one of the public–private partnership models targeting the discovery and development of new medicines, including antimicrobials. It is a joint undertaking between the European Commission and the European Federation for Pharmaceutical Industry and Associations, and has invested more than EUR660 million in the development of antibacterial agents [40]. Its targeted programme, called New Drugs for Bad Bugs (ND4BB), focuses on all the different stages of antimicrobial drug development, from drug discovery to clinical development, in order to push forward several promising molecules in the pipeline. Through one of its seven projects, called DRIVE-AB, ND4BB also targets the implementation of new business models and the responsible use of antibiotics. New and better business models are needed to serve as an incentive for the pharmaceutical industry to invest in the development of new antimicrobials. The relatively short course of treatment with antibiotics, compared with treatment regimens in oncology or chronic illnesses, does not deliver the same profit. The spread of antibiotic resistance and the promotion of prudent and restricted antibiotic use in order to preserve antibiotics for longer make it challenging to obtain a profitable economic model that can drive the development of new antibacterial molecules (table 2).

Alternatives to antibiotics

Nineteen alternatives to antibiotics have been identified to date, including antibodies, probiotics, bacteriophages, vaccines and antibiofilm peptides [41]. Within ND4BB, IMI has

Table 2. Anti-infectives in the final phases of clinical development

Anti-infective agent	Estimated indications	Ongoing RCTs
MEDI4893 (monoclonal antibody)	Prevention of *Staphylococcus aureus* VAP	Phase II and III clinical studies
MEDI3902 (monoclonal antibody)	Prevention of *Pseudomonas aeruginosa* VAP	Phase II; phase III (planned); phase I to assess the safety and pharmacokinetics in children (planned)
Aztreonam–avibactam	cIAIs, cUTIs and HAP/VAP, caused by metallo-β-lactamase-producing Gram-negative pathogens	Phase II; phase III (planned)
Imipenem–cilastatin–relebactam (MK-7655)	cIAIs, cUTIs and HAP/VAP, caused by MDR Gram-negative pathogens	Phase II in patients with cIAIs; phase III in patients with pneumonia
Meropenem–vaborbactam (formerly RPX7009)	Severe infections caused by MDR Gram-negative pathogens	Phase III to evaluate the safety, efficacy and tolerability in patients with cUTIs
S-649266 (siderophore cephalosporin)	Severe infections caused by MDR Gram-negative pathogens	Phase III in patients with HAP/VAP, cIAIs and cUTIs
Plazomicin (derivative of sisomicin)	Severe infections caused by MDR Gram-negative pathogens	Phase II to evaluate the safety and efficacy of plazomicin *versus* levofloxacin in cUTIs (completed); phase III
Finafloxacin	LRTIs, UTIs and SSTIs	Phase I (completed); phase II trials for uncomplicated and complicated UTIs and *Helicobacter pylori* infection
Delafloxacin	MRSA infections	Phase II in patients with LRTIs
Eravacycline	Severe infections caused by MDR Gram-negative and Gram-positive pathogens	Phase I (completed); phase II and phase III clinical trials in adult hospitalised patients with cIAIs

cIAI: complicated intra-abdominal infection; (c)UTI: (complicated) urinary tract infection; SSTI: skin and soft tissue infection.

funded several projects that aim to push forward the clinical development of monoclonal antibodies for the prevention and treatment of LRTIs [40, 42]. A promising monoclonal antibody, called MEDI4893, is currently being evaluated in a phase II clinical study for the prevention of *Staphylococcus aureus* pneumonia in mechanically ventilated patients (ClinicalTrials.gov, trial number NCT02296320). In pre-clinical studies, the parent molecule of MEDI4893 increased survival and reduced bacterial numbers in the lungs and kidneys of infected mice, and protected against diverse *S. aureus* clinical isolates [43, 44].

 https://doi.org/10.1183/2312508X.10006116

Another alternative molecule in clinical development is MEDI3902, a multifunctional bispecific monoclonal antibody targeting the pathogenic components PsI and PcrV of *P. aeruginosa* [40, 45, 46]. A phase II trial of MEDI3902 is currently being conducted to quantify the efficacy and safety of the compound in subjects at high risk of developing *P. aeruginosa* pneumonia (ClinicalTrials.gov, trial number NCT02696902). This study will include pre-emptive treatment with MEDI3902 in ICU patients colonised with *P. aeruginosa*. A phase III trial is planned for the near future [40], as is a phase I study to assess the safety and pharmacokinetics of MEDI3902 in children. If antipseudomonal monoclonal antibodies such as MEDI3902 prevent pneumonia in mechanically ventilated patients, they may also reduce antibiotic use in this population.

The expectations of bacteriophages for the treatment of bacterial infections have grown in recent years [47]. There have been several studies evaluating adjunctive phage treatment in various infections, such as chronic sinusitis refractory to antibiotics [48]. Bacteriophage therapy might be used as an alternative in patients with cystic fibrosis, as well as an additive to antibiotic regimens in HAP/VAP [49]. These and other alternatives may complement or replace antibiotic treatment in the future.

Antibiotics in the final phases of clinical development

This category is dominated by combinations of approved β-lactams with investigational β-lactamase inhibitors (figure 1).

β-Lactams and β-lactamase inhibitors

A promising compound targeting carbapenemase-producing *Enterobacteriaceae*, and more specifically metallo-β-lactamase producers, is aztreonam–avibactam. *In vitro* studies showed that aztreonam–avibactam provided synergy in antimicrobial activity against multiple β-lactamase-expressing strains with a wide MIC range [50]. Avibactam protects aztreonam from hydrolysis and enhances the antimicrobial activity against β-lactamase-producing strains. This synergistic combination is currently in phase II clinical development (ClinicalTrials.gov, trial number NCT02655419) and a phase III study is in preparation [40]. If successful, aztreonam–avibactam could be used for the treatment of severe infections, such as cIAIs, cUTIs and HAP/VAP, caused by metallo-β-lactamase-producing Gram-negative pathogens.

Imipenem–cilastatin–relebactam is another combination of already approved β-lactams with a new β-lactamase inhibitor. Relebactam (MK-7655) is a novel β-lactamase inhibitor, similar to avibactam, for the treatment of MDR Gram-negative infections when combined with imipenem. Unlike avibactam, relebactam does not have activity against the class D enzymes often produced by *A. baumannii* [51, 52]. Nevertheless, the combination is effective against carbapenem-resistant Gram-negative organisms, in particular *K. pneumoniae* carbapenemases (KPCs) [53], and was evaluated in a phase II trial in patients with cIAIs [54]. A phase III study evaluating the efficacy and safety of imipenem–cilastatin–relebactam for treating pneumonia is underway and will target patients with HAP/VAP caused by imipenem-resistant bacteria (ClinicalTrials.gov, trial number NCT02452047).

A relatively similar combination is that of meropenem with the serine β-lactamase inhibitor vaborbactam (formerly RPX7009). Vaborbactam restored meropenem activity in the

majority of cases in an *in vitro* study [55]. Meropenem–vaborbactam appears to be most effective against class A carbapenemases, such as KPCs, and is less potent against metallo-β-lactamase producers. A recent phase I study demonstrated the safety and tolerability of vaborbactam [56]. As a consequence of another phase I clinical trial of a similar combination (biapenem–vaborbactam), meropenem–vaborbactam proceeded directly to the next stages of clinical development [57]. This combination is currently undergoing phase III clinical trials to evaluate the safety, efficacy and tolerability in patients with cUTIs (ClinicalTrials.gov, trial number NCT02168946).

Another combination that is being investigated is ceftaroline–avibactam. A study conducted in four European medical centres suggested that avibactam enhances the activity of ceftaroline fosamil against *Enterobacteriaceae* and *P. aeruginosa* [58]. However, avibactam had no impact on the activity of ceftaroline against staphylococci, streptococci and *A. baumannii*. Nevertheless, avibactam broadens the spectrum of activity of ceftaroline and the combination is still to be explored.

The novel molecule S-649266, a catechol-substituted siderophore cephalosporin, appears to be promising for the treatment of various carbapenem-resistant infections, including LRTIs. There is pre-clinical evidence that S-649266 has potent activity against a wide range of Gram-negative pathogens, including MDR strains such as producers of KPC and New Delhi metallo-β-lactamase [59, 60]. In addition, S-649266 demonstrates activity against non-β-lactamase-mediated resistance including efflux pump and porin channel mutations. S-649266 is designed to exploit the iron uptake system of Gram-negative bacteria. It binds to iron, which is then absorbed by Gram-negative bacteria, actively transporting S-649266 through their outer membrane into the periplasmic space where it binds to penicillin-binding proteins. The molecule is currently in phase III of clinical development and is being evaluated in patients with HAP/VAP, cIAIs and cUTIs (ClinicalTrials.gov, trial number NCT02714595).

Aminoglycosides

Plazomicin is a novel aminoglycoside derivative of sisomicin [57, 61]. It is similar to other aminoglycosides such as amikacin, gentamicin and tobramycin, but is unaffected by aminoglycoside-modifying enzymes. Plazomicin is a molecule with good *in vitro* activity against carbapenem-resistant isolates. Resistance to plazomicin has already been described in *Enterobacteriaceae* strains with 16S ribosomal RNA methyltransferase, which modifies the ribosomal site that binds plazomicin [62]. A phase II trial evaluated the safety and efficacy of plazomicin *versus* levofloxacin in treating cUTIs [63]. Phase III trials have recently been completed (ClinicalTrials.gov, trial numbers NCT02486627 and NCT01970371) and data is under review and is expected to be published shortly.

Fluoroquinolones

Several fluoroquinolones, such as avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and the nonfluorinated nemonoxacin, are being investigated [64]. These agents have an antibacterial effect against ciprofloxacin-resistant pathogens. Among these molecules, finafloxacin deserves most attention, as, unlike other quinolones, it has good antibacterial activity under acidic conditions, which could be advantageous in the treatment of infections in acidic anatomical sites, such as respiratory and urinary tracts, skin and

 https://doi.org/10.1183/2312508X.10006116

intra-abdominal sites [64]. Finafloxacin also appeared to be more effective against *L. pneumophila* than ciprofloxacin [65]. A phase I study confirmed the safety and tolerability of this compound [66]. Finafloxacin has already been approved in the USA as a suspension for the treatment of acute otitis externa [67]. Phase II trials of oral and/or *i.v.* formulations demonstrated a good safety and tolerability profile in humans for the treatment of UTIs. However, more data from clinical trials are needed to confirm these preliminary results [68].

Delafloxacin [31] is a potent anti-MRSA drug with a unique dual mechanism of DNA target inhibition, which reduces the probability for selection of resistant mutants *in vitro* [69]. It has good coverage of both Gram-positive and Gram-negative pathogens. Phase II studies evaluating delafloxacin in the treatment of LRTIs yielded good eradication rates for *H. influenzae*, *Haemophilus parainfluenzae*, *S. aureus* and *S. pneumoniae* [70, 71]. Delafloxacin presents broad-spectrum activity against many of the pathogens causing CAP and HAP. This, together with the possibility of oral use, reduced selection of resistance and good tolerability, makes this compound promising for the treatment of LRTIs.

Tetracyclines

Eravacycline is a novel fluorocycline active against a wide range of Gram-negative and some Gram-positive species, as it evades tetracycline resistance mechanisms, such as efflux pumps and ribosomal protection proteins [72]. Eravacycline was found to be more potent than tigecycline against carbapenem-resistant *Enterobacteriaceae* and *A. baumannii* [73, 74], and recent data demonstrated that eravacycline is effective against colistin-resistant isolates [75]. However, similar to tigecycline, eravacycline is not effective against *P. aeruginosa*. In a phase I study, eravacycline achieved concentrations 6- and 50-fold higher in epithelial lining fluid and in alveolar macrophages, respectively, than in plasma [76]. Eravacycline had a similar efficacy to ertapenem in phase II and phase III clinical trials in adult hospitalised patients with cIAIs [77, 78]. Further studies are needed to demonstrate the advantages of eravacycline over other drugs used in the treatment of cUTIs and LRTIs. In murine models, eravacycline was as effective as linezolid and more effective than vancomycin for MRSA lung infections [79]. The possibility of using either an oral or an *i.v.* formulation would make eravacycline attractive for de-escalation therapy in patients with MDR infections [31].

Conclusions

The rapidly spreading menace of antimicrobial resistance has wiped many antibiotics off the treatment regimens for infections, including LRTIs. The pandemicity of certain bacterial clones, plasmids and genes, and the lack of rapid diagnostic tests, combined with a lack of screening and an overall failure to rapidly detect resistant isolates, have facilitated the spread of MDR organisms, which has been accelerated by increased antibiotic selective pressure and ineffective antimicrobial stewardship and infection control measures.

The antibiotic pipeline is almost empty. Although some promising molecules have appeared in recent years and are already being used in clinical practice, there is clearly an unmet public health need for new antibacterial classes. Many pharmaceutical companies have been reluctant to invest in antibiotic drug discovery and development in the past two decades, mainly because of the perceived low economic return of investment. One of the most ambitious and substantial investments of resources in this field was made by the IMI

programme [40]. Collaborative funding into the research and development of antibiotics is needed and represents a substantial long-term investment in public health globally. One of the main aims of the platform for clinical trials created by the IMI projects is to boost the drug discovery and clinical development of anti-infectives and to offer the market new compounds as soon as possible [40]. More collaborative funding opportunities, such as IMI, are needed to mitigate the problem of antimicrobial resistance. Funding of research in this field has been recognised by both the UK and US governments [1, 40], and is on the agenda of global organisations such as the United Nations and World Health Organization [80]. A sustainable clinical trial infrastructure is needed to support trials of antimicrobials and to make clinical development less problematic for the pharmaceutical industry. A multidisciplinary network, such as the one created under the ND4BB programme, that would deliver crucial data for the registration of new antibacterial agents could substantially improve the efficiency of anti-infective trials. Shortening the time for clinical development by collecting various data from observational studies in the field of infectious diseases and implementing adaptive clinical trial designs would lower the investment required for the clinical development of new antimicrobials. Similar to the clinical trial network of the European Organisation for Research and Treatment of Cancer, created in 1962, there is a need, now more than ever, for a high-quality clinical trial network for evaluating new anti-infective treatments. Such a joint effort would represent a substantial leap forward in the fight against antimicrobial resistance.

For the time being, there is an unmet medical need for new antibiotic molecules for treating infections caused by resistant bacteria. The declining interest of the pharmaceutical industry to engage (and invest) in antibiotic discovery is one of the main reasons for the pipeline running dry [81].

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Disclosures: None declared.

Chapter 19

Combination antibiotic therapy and synergy in HAP and VAP

Rodrigo Cavallazzi[1] and Julio A. Ramirez[2]

HAP and VAP are common and associated with poor outcomes. They are characterised by a high prevalence of MDR organisms. As a result of these factors, combination therapy has been advocated for these conditions and this is the focus of our chapter. We present the theoretical advantages of combination therapy, review the clinical evidence related to combination therapy in HAP and VAP with an emphasis on RCTs where they were available, summarise the recommendations of the current guidelines for the management of HAP and VAP, and discuss the use of de-escalation therapy. We conclude with a description of our approach at University of Louisville Hospital, where we use combination therapy in all patients with HAP and VAP. We use empiric Gram-negative combination therapy with a β-lactam and a quinolone with the goal to increase the initial antimicrobial spectrum, and we use vancomycin or linezolid for coverage against MRSA. Microbiological studies are always used and de-escalation of therapy follows once these studies become available.

Cite as: Cavallazzi R, Ramirez JA. Combination antibiotic therapy and synergy in HAP and VAP. *In:* Aliberti S, Chalmers JD, Pletz MW, eds. Anti-infectives and the Lung (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 302–311 [https://doi.org/10.1183/2312508X.10006216].

HAP and VAP are a major public health problem. They are characterised by the presence of MDR pathogens, and high morbidity and mortality. For example, in a prospective cohort study, 400 pathogens were isolated from 327 cases of VAP. Of these, Gram-positive cocci and Gram-negative bacilli accounted for 32% and 59%, respectively. Oxacillin-resistant *Staphylococcus aureus* was isolated in 18%, *Pseudomonas aeruginosa* in 18% and *Acinetobacter* spp. in 8% of the cases. In the 261 cases of HAP, 270 pathogens were identified. Of these, Gram-positive cocci and Gram-negative bacilli accounted for 43% and 40%, respectively. Oxacillin-resistant *S. aureus* was isolated in 20%, *P. aeruginosa* in 9% and *Acinetobacter* spp. in 3% of the cases [1]. This study demonstrated that while there is some variation in the prevalence of *P. aeruginosa* infection, MDR pathogens are similarly present in a high proportion of both HAP and VAP. A systematic review identified observational studies that reported mortality in VAP that ranged from 14% to 78%. The

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relative risk of death was 1.27 (95% CI 1.15–1.39) [2]. In a multicentre study of patients outside the ICU with HAP, the mortality was 26% [3].

Here, our focus is on the use of combination therapy for the treatment of HAP and VAP. We used the same definitions of prior guidelines, separating HAP from VAP. In HAP, the pneumonia occurs 48 h after admission and was not incubating at the time of admission. In VAP, the pneumonia occurs in a patient receiving invasive mechanical ventilation for at least 48 h [4].

Theoretical advantages for combination therapy

Five main theoretical reasons can be identified for the use combination therapy in HAP and VAP (table 1). Here, we outline the five theoretical justifications; however, it is important to emphasise they are not necessarily supported by clinical evidence.

First, combination therapy can be used to broaden the initial antibiotic spectrum and thus minimise the chance of lack of initial coverage for the infection. The importance of adequate initial coverage is highlighted by a number of studies showing increased mortality if the initial empiric treatment is inadequate. As an example, Luna *et al.* [5] conducted a prospective observational study in 132 patients with VAP who underwent bronchoscopy with BAL. Patients who received inadequate initial antibiotic therapy had a mortality of 91% compared with 38% in those who received adequate therapy ($p<0.001$). Half of the deaths in patients with a positive BAL occurred within 48 h from the bronchoscopy, before the microbiology results were available [5]. In a retrospective cohort study of 1171 patients with pneumonia or sepsis caused by *Acinetobacter baumannii*, multidrug resistance, defined as resistance to at least one agent in at least three classes of antimicrobials, was present in most cases. Patients with MDR organisms received more inadequate therapy. The risk of death almost doubled in those who received inadequate empiric therapy [6].

Second, combination therapy can be used to obtain synergy against a particular pathogen. Tamma *et al.* [7] define synergy between two antimicrobial agents as an increase of >2 log in the *in vitro* bactericidal activity compared with the *in vitro* bactericidal activity of each isolated agent. An example of synergy is the combination of an agent active against the cell wall with an aminoglycoside to obtain synergy against Gram-negative rods. The effect stems from increased cell wall permeability to aminoglycoside in the presence of a β-lactam antibiotic. Another classic example is the combination of a β-lactam antibiotic with a

Table 1. Mechanisms and examples of use of combination therapy in HAP and VAP

Mechanism	Example(s)
Broadening empiric antibiotic spectrum	Use of two antipseudomonal antimicrobials of different classes as empiric treatment for HAP/VAP
Synergy	β-Lactam with aminoglycoside
Prevention of resistance	Well established in TB; β-lactam with aminoglycoside in sepsis
Immunomodulation	Azithromycin in combination with other antibiotics
Blocking bacterial toxin synthesis	Addition of clindamycin to the antibiotic regimen in staphylococcal infection

β-lactamase inhibitor. The latter in general does not have much of an effect against pathogens, but it enables the inactivation of β-lactamase produced by some bacteria and consequently allows the β-lactam antibiotic to act against the pathogens. A synergistic effect can also be obtained when two antibiotics act sequentially in a metabolic pathway [8].

Third, combination therapy can be used with the goal of preventing the development of resistance to a particular antimicrobial. For instance, an early study found that methicillin-resistant *Staphylococcus epidermidis* rapidly developed resistance to rifampin in an *in vitro* setting. However, the addition of vancomycin or a cephalosporin prevented the development of this resistance [9]. Clinically, the combined use of antimicrobials to prevent resistance has been well established in the treatment of TB [8, 10].

Fourth, a second antimicrobial agent can be added for its immunomodulation effects. An experimental study showed that macrolides can decrease monocyte and neutrophil transendothelial migration. Additionally, macrolides can also decrease the levels of pro-inflammatory chemokines [11]. Macrolides modulate the production of cytokines on the bronchial epithelial cells [12]. In cultured human bronchial epithelial cells, release of inflammatory mediators, such as IL-6, IL-8 and soluble intercellular adhesion molecule-1, was induced by *Haemophilus influenzae* endotoxin. Addition of erythromycin decreased both the release of these inflammatory mediators and neutrophil chemotaxis [13]. There is a large body of data on the use of macrolides in CAP. Observational studies indicate an improvement in outcomes with the use macrolides in CAP, although clinical trials did not consistently demonstrate a benefit [14–16]. There are fewer studies evaluating the role of macrolides in HAP or VAP.

Fifth, a second antimicrobial agent can be added to block bacterial toxin synthesis. In some patients with pneumonia and sepsis, poor clinical outcomes may be mediated primarily by the bacterial production of toxins. In these patients, combination therapy with the addition of an antibiotic that inhibits bacterial protein synthesis may be indicated. This is the case, for instance, of clindamycin in the setting of *S. aureus* infection. The *in vitro* release of staphylococcal toxins is lower with clindamycin compared with ceftriaxone [17]. In another study, both clindamycin and linezolid substantially suppressed expression of Panton–Valentine leukocidin by MRSA in an *in vitro* experiment [18]. The gene for this toxin is particularly prevalent in community-acquired MRSA [19].

Clinical studies

Empirical treatment

In a prospective study of 113 patients with HAP, cefoperazone monotherapy was compared with combination therapy (either clindamycin–gentamicin or cefazolin–gentamicin) [20]. 29 patients were intubated at enrolment. The cure rate was 87% in the monotherapy group and 72% in the combination group ($p=0.069$). Limitations of this study were the lack of β-lactam antibiotic in one of the control arms and absence of blinding. Additionally, the investigators were able to choose the control arm based on the microbiology results.

In a double-blind multicentre clinical trial, 781 adult patients with HAP were randomised to ceftobiprole or ceftazidime plus linezolid [21]. Of these patients, 210 had VAP. The primary outcome was clinical cure at the test-of-cure visit. In the VAP population,

 https://doi.org/10.1183/2312508X.10006216

combination therapy led to a higher cure rate (37% *versus* 23%, 95% CI of difference 1.5–26%) and microbiological eradication rate (50% *versus* 30%, 95% CI of difference 0.4–38.8%). There was no significant difference in mortality between the two groups. In the HAP population, there was no statistically significant difference in cure rate, microbiological eradiation rate or mortality. A potential limitation of this study is that patients with severe renal impairment or hepatic dysfunction were excluded, limiting the generalisability of the results.

In a prospective open-label study performed in 14 Spanish ICUs, 140 adult patients with VAP were randomised to meropenem or ceftazidime plus amikacin [22]. The study aimed to compare the clinical and microbiological efficacy and safety between the two treatment arms. The two groups had a similar clinical response (68% *versus* 55%) in the intention-to-treat analysis. Monotherapy led to higher bacteriological eradication (75% *versus* 53%; odds ratio (OR) 1.40, 95% CI 1.02–1.92; p=0.030). There was no significant difference in mortality between the two groups. Limitations of this study included the small sample size and the lack of clear delineation of the primary outcome. Furthermore, the treatments were not blinded.

In a single-centre randomised trial, 74 adult patients with VAP were randomised into three groups: cefepime, cefepime plus amikacin and cefepime plus levofloxacin [23]. The study aimed to assess not only clinical outcomes but also changes in biological variables. There was no difference in the evolution of biological variables such as CRP, leukocytosis, temperature and arterial oxygen tension/inspiratory oxygen fraction ratio. Additionally, there was no significant difference in ICU length of stay, ventilator-free days or mortality among the three groups. Limitations of this study included the small sample size and lack of blinding.

In a multicentre randomised trial that included 28 ICUs in Canada and USA, 740 patients with VAP were randomised to meropenem plus ciprofloxacin or meropenem [24]. The primary outcome was 28-day mortality. The relative risk of death within 28 days in the combination group compared with the monotherapy was not significantly different (1.02, 95% CI 0.78–1.42; p=0.74). Other outcomes, such as length of ICU and hospital stay and clinical and microbiological response, were similar between the two groups. In a subgroup analysis, patients with MDR Gram-negative bacilli on enrolment who received combination therapy had a trend toward lower hospital length of stay and 28-day mortality. A limitation of the study is that there was no blinding. Also, it should be noted that this study had a low prevalence of *Pseudomonas*, MRSA and other MDR pathogens, which may be due to the exclusion criterion of prior colonisation or infection by MRSA or *Pseudomonas*.

Two meta-analyses found similar results with regard to the impact of combination therapy in VAP. In 2008, a systematic review and meta-analysis evaluated the effectiveness of different antibiotic regimens for the empiric treatment of VAP [25]. The pooling of eight studies showed no difference in mortality with monotherapy *versus* combination therapy (relative risk 0.94, 95% CI 0.76–1.16). A 2016 Cochrane systematic review and meta-analysis evaluated the impact of different empirical antimicrobial regimens on the mortality of patients with VAP [26]. Four randomised clinical trials were included in a meta-analysis comparing monotherapy *versus* combination therapy and there was no difference in mortality (OR 0.97, 95% CI 0.73–1.30). Another Cochrane meta-analysis from 2014 included clinical trials that compared β-lactam monotherapy *versus* β-lactam plus an aminoglycoside in patients with sepsis [27]. The pooling of 12 studies, which included 1431

patients, showed no difference in mortality with monotherapy *versus* combination therapy (relative risk 0.97, 95% CI 0.73–1.3). It should be highlighted that the latter meta-analysis did not specify that patients had to have pneumonia.

Taken together, the above clinical trials provided mixed results and failed to demonstrate a clear benefit of combination therapy. The studies have a number of limitations as outlined and are heterogeneous since different antimicrobial regimens were used. In some trials, there was no clear distinction between HAP and VAP, and in other trials there was a mix of HAP and VAP in the patient population.

Synergy

A few observational studies have evaluated the synergistic effect of combination antibiotic therapy on clinical outcomes. These studies, however, were not conducted in patients with HAP or VAP. Additionally, they provided conflicting results and no firm conclusion can be drawn as to the clinical benefit of combination therapy regimens that show *in vitro* synergy [28–30].

Prevention of resistance

A number of clinical trials have assessed the combination of β-lactam with aminoglycoside against β-lactam monotherapy [31–38]. Not all of these studies included solely patients with pneumonia. According to a meta-analysis from 2005, β-lactam monotherapy was not associated with a higher rate of antimicrobial resistance (OR 0.90, 95% CI 0.56–1.47), and led to a lower rate of superinfections (OR 0.62, 95% CI 0.42–0.93) and treatment failures (OR 0.62, 95% CI 0.38–1.01) [39].

Immunomodulation

Giamarellos-Bourboulis *et al.* [40] conducted a double-blind clinical trial in 200 patients with VAP who were randomised to either clarithromycin or placebo. The clarithromycin group had faster resolution of VAP and weaning from the ventilator, but the 28-day mortality from sepsis was not different. A secondary analysis of the same cohort of patients showed that the clarithromycin-treated group had an increased pro-inflammatory state as measured by the levels of circulating markers. The authors of the study suggested that clarithromycin attenuated the pro-inflammatory *versus* anti-inflammatory imbalance by reversing sepsis-induced immunoparalysis [41]. Most data, however, indicate a predominantly anti-inflammatory effect of macrolides [11, 42]. While the results of these studies showing an immunomodulation effect of macrolides are promising, we believe that an additional multicentre well-powered clinical trial is needed before a firm recommendation can be made on the use of macrolides in VAP.

Current guidelines recommendations

In patients with diagnosis of VAP, the most recent USA guidelines suggest empiric therapy with two antipseudomonal antimicrobials of different classes in the presence of any of the following: a risk factor for antimicrobial resistance, units with >10% of Gram-negative isolates resistant to a monotherapy agent or ICUs with unknown susceptibilities rates [43]. An added agent against MRSA (vancomycin and linezolid) is suggested in the presence

 https://doi.org/10.1183/2312508X.10006216

of any of the following: a risk factor for antimicrobial resistance, units with >10–20% of *S. aureus* isolates that are methicillin resistant or ICUs with unknown susceptibilities rates. Risk factors for MDR pathogens in VAP include receipt of intravenous (*i.v.*) antibiotic over the last 90 days, septic shock, acute respiratory distress syndrome before VAP, ⩾5 days of hospitalisation before VAP and acute renal replacement therapy before VAP onset [43].

In patients with a diagnosis of HAP, the USA guidelines suggest empiric therapy with two antipseudomonal antimicrobials if the patient received antimicrobial within the last 90 days or if there is a high risk of mortality, which includes requirement for invasive mechanical ventilation and septic shock. An added agent against MRSA (vancomycin and linezolid) is suggested in the presence of any of the following: receipt of *i.v.* antibiotic over the last 90 days, units with >20% of *S. aureus* isolates that are methicillin resistant, units with unknown MRSA prevalence or high risk of mortality [43].

In both HAP and VAP, the guidelines recommend dual coverage against *P. aeruginosa* if the patient has structural lung disease predisposing to *P. aeruginosa* infection, such as bronchiectasis or cystic fibrosis [43].

The guidelines further recommend monotherapy in both HAP and VAP in the setting of known *P. aeruginosa* infection using an antibiotic to which the pathogen is susceptible. However, if the patient has septic shock or high risk for death, the guidelines suggest the use of two antimicrobials to which the pathogen is susceptible [43].

Importance of de-escalation therapy

Overtreatment with antimicrobials leads to resistance and superinfections. This was highlighted by a study that enrolled patients in the ICU with new-onset pulmonary infiltrate but low suspicion for pneumonia according to a scoring system. Patients were randomised to *i.v.* ciprofloxacin (experimental arm: 39 patients) for 3 days or antimicrobial therapy at the discretion of the treating physician (control arm: 42 patients). In the experimental group, a re-evaluation was performed at day 3 and antibiotic was discontinued if the scoring system indicated low likelihood of pneumonia. Antibiotics were continued for >3 days in 97% of the control arm *versus* 28% of the experimental group. While there was no difference in mortality, patients in the experimental group had less development of antimicrobial resistance and/or superinfection (15% *versus* 35%; p=0.017). Additionally, among those who survived, the experimental group had a lower length of ICU stay (mean 9.4 *versus* 14.7 days; p=0.04) [44].

A strategy to avoid unnecessary exposure to antimicrobials is the implementation of de-escalation therapy, which represents the narrowing of the initial broader spectrum coverage, or the discontinuation of one or more antimicrobial, so that the antimicrobial therapy is targeted to the pathogen identified in the microbiology studies (table 2). In a prospective observational study of 398 ICU patients with suspected VAP, de-escalation therapy was performed in 22% of the patients and was associated with lower mortality (17% *versus* 23.7% in the no de-escalation group; p=0.001) [45]. In another prospective observational study in 143 patients with VAP confirmed by lower respiratory tract culture, de-escalation therapy was performed in 58 (40.5%) patients. Patients who underwent de-escalation therapy had lower 28-day mortality (12% *versus* 43.5%; p<0.05)

Table 2. Definition of de-escalation therapy

- Discontinuation of one or more antimicrobials based on the results of the microbiology studies
- Narrowing the spectrum of an antimicrobial based on the results of the microbiology studies
- Shortening the therapy if patient shows signs of clinical improvement

and lower hospital length of stay (23.7 *versus*. 29.8 days; p<0.05) [46]. Another prospective observational study found that de-escalation therapy occurred less often with late-onset VAP (compared with early-onset VAP) and when there was growth of MDR organisms [47].

All of these studies were heterogeneous in their design and the definition of de-escalation therapy was not uniform. However, they provide evidence that the application of de-escalation in the ICU is feasible and leads to better outcomes with less antibiotic exposure.

Conclusions

The current USA guidelines place strong emphasis on the use of a hospital antibiogram to guide therapy in HAP/VAP [43]. We agree that the use of a hospital ICU antibiogram can be extremely helpful in the selection of empiric therapy; however, we currently recognise a number of barriers to the widespread use of hospital antibiograms. First, most hospitals do not generate antibiograms. For instance, Stein *et al.* [48] conducted a survey of 110 hospitals in North Carolina, USA, to assess pneumococcal resistance to antibiotics. Only 60 hospitals replied to the survey. Of these, 11 (18%) did not provide a hospital antibiogram. In nine of these hospitals, there was no on-site susceptibility testing. Second, hospital antibiogram reports should be standardised. In a survey of 100 hospitals in Michigan, USA, serious errors were identified in 99 (28%) out of 239 analysed cumulative antibiograms. These errors included, for instance, reporting clindamycin for the treatment of *Enterococcus* infection [49]. Third, hospital antibiogram reports frequently contain data that mixes organisms that cause only colonisation with organisms that cause real infections, and mixes organisms obtained from inpatient and outpatient settings. Fourth, clinicians need to have ready access and be knowledgeable of the local antibiogram results. There is data showing this does seem to be the case. As an example, only 48% of the clinicians in a Veterans Affairs Hospital in the USA reported having reviewed the local antibiogram report in the past year. Only 10% of the clinicians used the antibiogram report most of the time and half of the clinicians did not use antibiograms to guide treatment decisions [50]. Fifth, the hospital antibiogram may not reflect the current situation the clinician is facing. To generate a comprehensive antibiogram, the microbiology department will require at least 6 months. Therefore, when analysing the antibiogram we are always looking at the past history of bacterial resistance in a particular unit. For instance, if there is recent outbreak of ESBL bacteria in an ICU, the clinician will need to adapt the empirical therapy to cover those organisms even though this may not be representative in the "current" hospital antibiogram. In these situations, the hospital antibiogram can produce misleading information and a false sense of security. As a result of these factors, we believe that the reliance of current USA guidelines on the evaluation of a hospital antibiogram meets logistical challenges. However, some of these challenges could be circumvented and generation of local antibiograms by hospitals should be pursued. Antibiograms can be

 https://doi.org/10.1183/2312508X.10006216

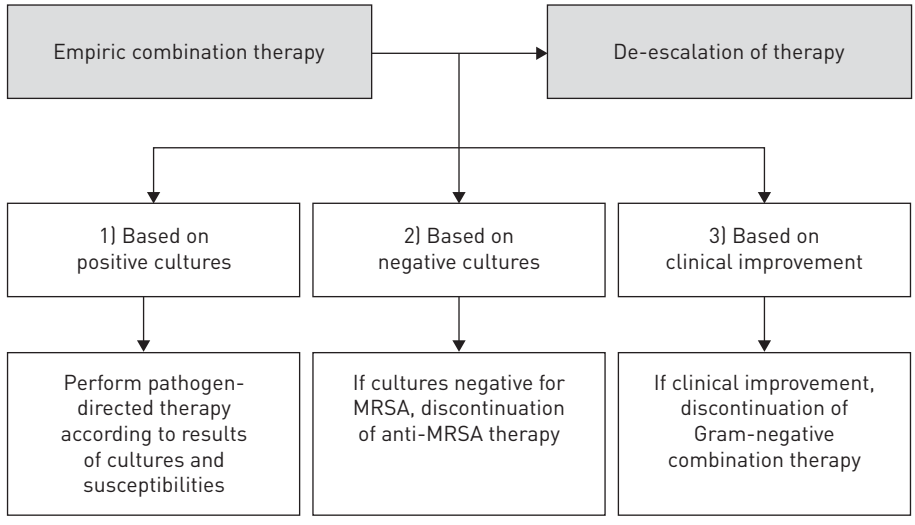
Empiric combination therapy
De-escalation of therapy
1) Based on positive cultures
2) Based on negative cultures
3) Based on clinical improvement
Perform pathogen-directed therapy according to results of cultures and susceptibilities
If cultures negative for MRSA, discontinuation of anti-MRSA therapy
If clinical improvement, discontinuation of Gram-negative combination therapy

Figure 1. Strategy for combination therapy and de-escalation in HAP and VAP.

helpful, for instance, in determining the additive gain of two classes of antibiotic in Gram-negative infection.

The approach of the authors for patients with HAP or VAP, at the University of Louisville Hospital, is the clinical approach of "hit early and hit hard" (figure 1). This approach translates to the use of initial empiric combination therapy for all patients with HAP or VAP regardless of the presence of risk factors. All patients are treated with combination therapy with at least one agent against *P. aeruginosa* and other Gram-negative bacteria and a second agent active against MRSA. The USA guidelines suggest to add anti-MRSA empiric therapy for VAP in units with >10–20% prevalence for methicillin resistance in the *S. aureus* isolates and to add anti-MRSA empiric therapy for HAP when the prevalence for methicillin resistance in the *S. aureus* isolates is >20% [43]. According to these recommendations, physicians who work in a hospital with a prevalence of 10% of methicillin resistance in the S. aureus isolates may not use anti-MRSA empiric therapy. This will translate to patients with MRSA HAP or VAP not receiving appropriate empiric anti-MRSA therapy. For these patients, even if anti-MRSA therapy is added once cultures are available, it may be too late to prevent patient clinical failure and likely death. Our approach is that any prior level of MRSA in the hospital is sufficient evidence to add empiric therapy against MRSA. We diligently obtain microbiological studies and de-escalate the antimicrobials once the results of these studies are available. In patients without MRSA isolated in respiratory samples, we discontinue anti-MRSA therapy.

With regard to empiric therapy for *P. aeruginosa,* we use the hospital antibiogram to guide the selection of the best β-lactam agent for empiric therapy against *P. aeruginosa* and other Gram-negative rods. Since we do not have a single β-lactam agent that is able to cover all Gram-negative rods, we use empiric Gram-negative combination therapy with a β-lactam and a quinolone with the goal to increase the initial antimicrobial spectrum. We follow the USA guideline recommendations regarding not to use aminoglycosides as single agents against *P. aeruginosa* [43].

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Disclosures: R. Cavallazzi has received personal fees from Cempra.

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Print ISSN: 2312-508X
Online ISSN: 2312-5098
Print ISBN: 978-1-84984-083-5
Online ISBN: 978-1-84984-084-2
March 2017
€60.00